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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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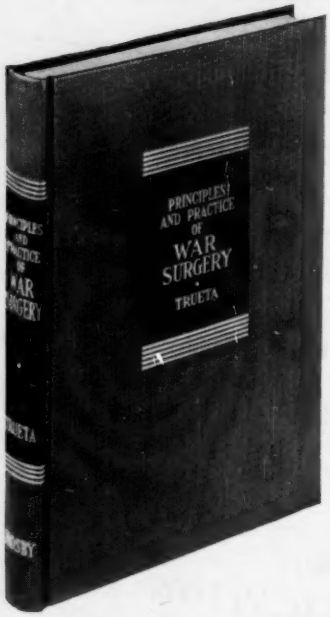

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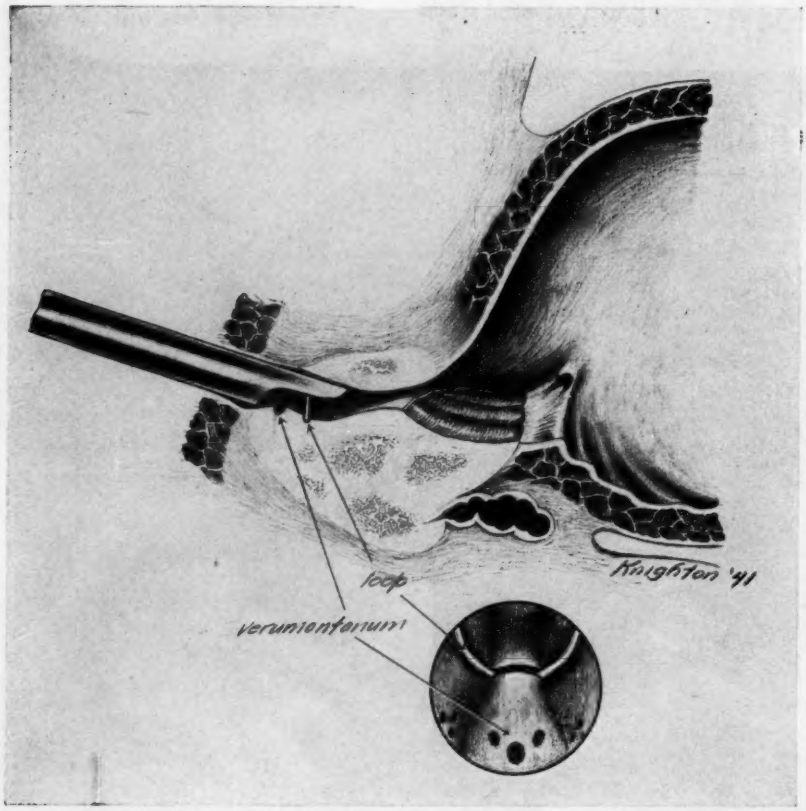

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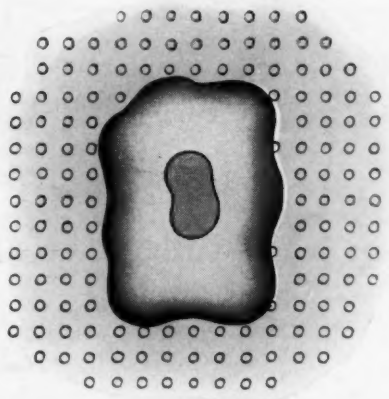

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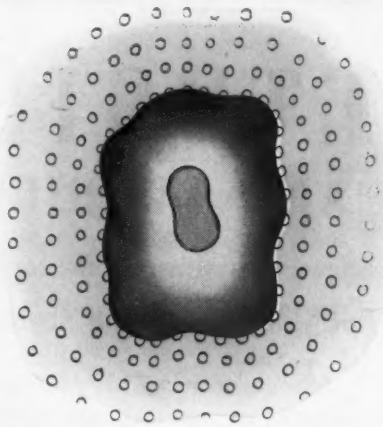

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SURGERY

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Original Communications

ACUTE CRANIOCEREBRAL TRAUMA

SURGICAL AND PATHOLOGIC CONSIDERATIONS BASED UPON 151 CONSECUTIVE AUTOPSIES

E. S. GURDJIAN,* M.D., J. E. WEBSTER, M.D., AND H. ARNKOFF,† M.D.
DETROIT, MICH.

THE material herein presented comprises the results of observations made upon post-mortem examinations of 151 patients who died following cranial trauma. The examinations were performed at the Wayne County Morgue, Detroit, Mich. They represented a consecutive, unselected group admitted to the morgue throughout a period of eight months, from July, 1939, to March, 1940. The hospital records of those patients who were hospitalized before death were also studied for pertinent correlations.

This analysis is not intended for statistical purposes, but it is an attempt to correlate the pathologic features and the surgical management of cases of head injury. A survey of the pathologic background should serve to amplify surgical and medical concepts of treatment.

Material.—Gross evidence of brain damage was found in every case, although in a few instances the pathologic changes were minimal (Fig. 1). Combinations of lesions were of frequent occurrence. For purposes of clarity, the pathologic findings were classified into main groups on the basis of the outstanding type of lesion present (Table I).

Age Distribution.—The well-recognized observation that the mortality rises with the higher age groups among patients with head injury is shown in Table II. Even though the incidence of major head injury is less in childhood, the evidence shows that children tolerate the effects of trauma much better than do patients in higher age groups.

*Department of Surgery, Wayne University College of Medicine, and Department of Neurosurgery, Grace Hospital. Major, U. S. Army.
†Medical Corps, U. S. Army.
Received for publication, June 3, 1942.

TABLE I

Fracture of the skull		112
Compound fractures		29
Gunshot etiology		18
No fractures		39
Epidural hemorrhages (surgical)		11
Associated with fracture	10	
Unassociated with fracture	1	
Epidural hemorrhages (small)		4
Acute subdural hematoma (surgical)		22
Acute subdural hematoma (small)		12
Chronic subdural hematoma		1
Massive intracerebral clot		1
Petechial hemorrhages	54	
With gunshot wounds	17	71
Contusions of the brain surface with softening		72
Cerebral fat embolism		2

TABLE II

AGE DISTRIBUTION

AGE GROUPS (YR.)	NUMBER OF CASES
Under 5	8
5 to 10	1
10 to 20	11
20 to 30	27
30 to 40	24
40 to 50	28
Over 50	52

TABLE III

CHART SHOWING RELATIONSHIP OF ETIOLOGY TO PATHOLOGY FOUND IN AUTOPSY SERIES

ETIOLOGY	NUMBER OF CASES	PATHOLOGY						
		EPIDURAL HEM.	SUBDURAL HEM.	SUBARACHNOID HEM.	MASSIVE INTRACEREBRAL HEM.	PETECHIAL HEM.	FRACTURE	CONTUSION
Fall	23	3	8*	5	0	11	15	12
Direct trauma	1	0	0	0	0	1	1	1
Auto accident	90	4	12	28	1	29	66	52
Electricity	2	0	0	1	0	2	0	0
Fights	6	1	2	0	0	3	4	5
Bullet wounds	18	—	—	—	—	17	18	—
Explosion	1	0	0	0	0	1	1	0
Train accidents	3	0	1	1	0	2	2	1
Auto-Bicycle accidents	5	3	0	1	0	4	4	1
Unknown cause of death	2	0	0	1	0	1	1	0
Total	151	11	23*	37	1	71	112	72

*One case of chronic subdural hematoma.

Etiology.—Direct blow to a fixed or nonfixed head is common. The head is usually injured by indirect blows; that is, the head in motion strikes a nonmoving or slower moving object. In either of the latter groups, multiple lesions occur as well as injuries to other parts of the

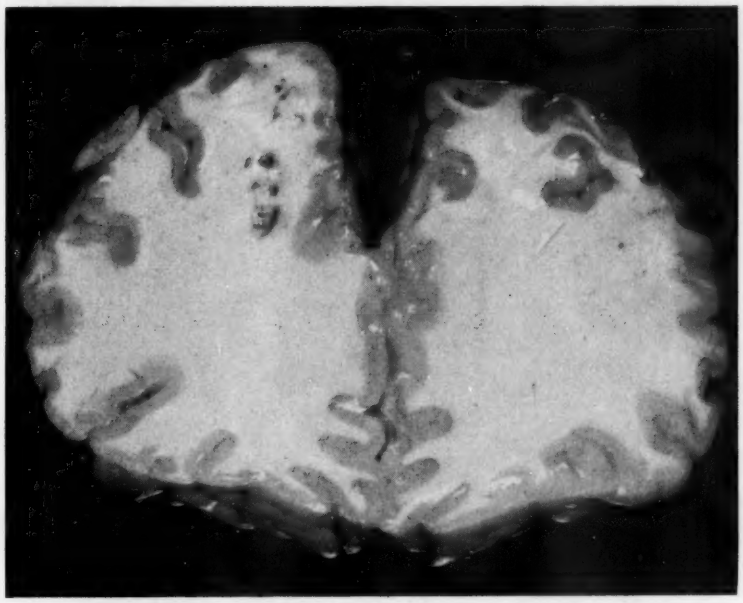

Fig. 1.—An example of minimal cerebral damage involving the frontal lobe. This patient, aged 35 years, was struck by an auto. There was no fracture of the skull. He survived injury for 7 days (associated injury, fractured tibia).

body (Fig. 2). Of interest in the tabulation of the causes of injury is the frequent association of epidural hemorrhage and bicycle accidents. In Table III the etiologic factors and the resultant pathologic changes have been correlated.

Time of Death.—In 133 cases, the time of death was classified and is shown in Table IV. Of note is the fact that sixty-one victims were dead

TABLE IV

TIME OF DEATH

TIME OF DEATH	NUMBER OF CASES
Dead on admission	61
1 hr.	2
2 hr.	5
3 hr.	12
5 hr.	5
10 hr.	5
15 hr.	2
20 hr.	5
30 hr.	7
2 days	6
3 days	5
4 days	3
5 days	1
Over 5 days	14

upon admission, while thirty-six died within twenty hours after entrance to the hospital, a group which represents 72.1 per cent of the total.

Fractured Skull.—Fracture of the skull was present in 112 instances. In twenty-nine the fracture was compounded; eighteen of the latter were caused by gunshot wounds. Head injury unassociated with fracture of

Fig. 2.—An example of profound cranial damage with comminution of the middle fossa and destruction of the left optic nerve. The fracture line extends from the left orbit and frontal region to the pituitary fossa and across the length of the petrous bone of the left side.

the skull occurred in thirty-nine patients. Of the instances in which a fracture was found to be present, the site of the fracture was localized to the anterior third of the skull in 22.9 per cent of the cases; to the middle third in 45.3 per cent, and to the posterior third in 32.7 per cent (Table V).

TABLE V

LOCALIZATION OF FRACTURE

LOCALIZATION	NUMBER OF CASES
Anterior 3rd	6
Middle 3rd	35
Posterior 3rd	18
Anterior and middle	11
Middle and posterior	11
Anterior, middle, and posterior	13

TABLE VI

CHART OF SITE OF CONTUSIONS

SITE	NUMBER OF CASES
Inferior frontal	R—24 L—25
Inferior temporal	R—23 L—22
Frontal (lateral and superior)	R—10 L— 9
Temporal (lateral and superior)	R—27 L—20
Parieto-occipital	R—10 L—12
Cerebellum and brain stem	R— 5 L— 4

The distribution of the fracture lines is more graphically represented in Fig. 3.

Cerebral Contusions.—An outstanding finding in the examination was the occurrence of contused areas of the cortex of the hemispheres (Fig. 4). There were 191 instances of such areas among seventy-two of the cases. For the sites of the contusions, see Table VI.

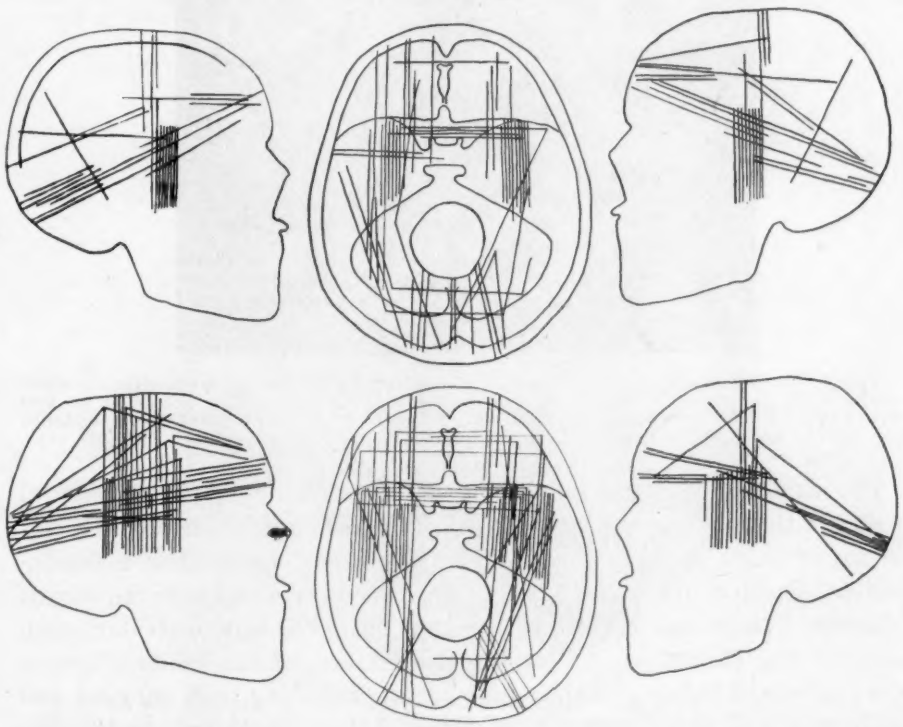

Fig. 3.—Diagrammatic representation of fractures in ninety-four cases. Right lateral, basal, and left lateral views are shown in two rows. The most common site of fracture is the middle third of the skull (45.3 per cent).

Fig. 5 demonstrates the aggregations of the areas involved by bruising of the brain. They are shown in upper and lower groups, to make the diagram more intelligible.

ACUTE SUBDURAL HEMORRHAGE

In this series, subdural hematoma of surgical proportions (about 30 Gm. and over) was found in twenty-two cases, and in twelve additional cases small hemorrhages in the subdural space were discovered. The latter includes cases of very minimal hemorrhages in the subdural space up to the amount of about 30 Gm. in size. The larger subdural hematomas were unilateral in each instance. In the group with insignificant subdural hemorrhage, there were four bilateral cases.

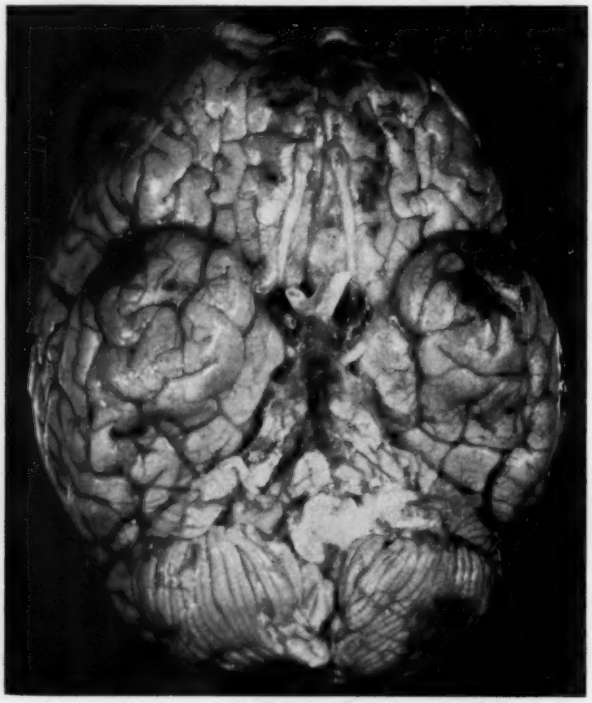

Fig. 4.—An example of multiple cerebral contusions located in commonly involved areas. This patient, aged 52 years, was involved in an automobile accident; he had a lucid interval and then progressive stupor. Bilateral trephines were made on the tenth day with evacuation of bilateral subdural hydromas. He expired the eleventh day.

The subdural hemorrhage occurred in the fronto-parieto-temporal region in the greatest majority of cases (Fig. 6). In one there was a collection of blood in the region of the optic chiasm. In another, a fronto-parietal hematoma extended between the hemispheres and over the corpus callosum. There was one case of hematoma over the left cerebellar hemisphere. The fronto-parieto-temporal localization of the subdural lesion was evident in thirty of thirty-four cases (including both surgical and small subdural hemorrhages). A frontoparietal trephine opening two inches on either side of the midline would have uncovered the clot in each of the thirty cases.

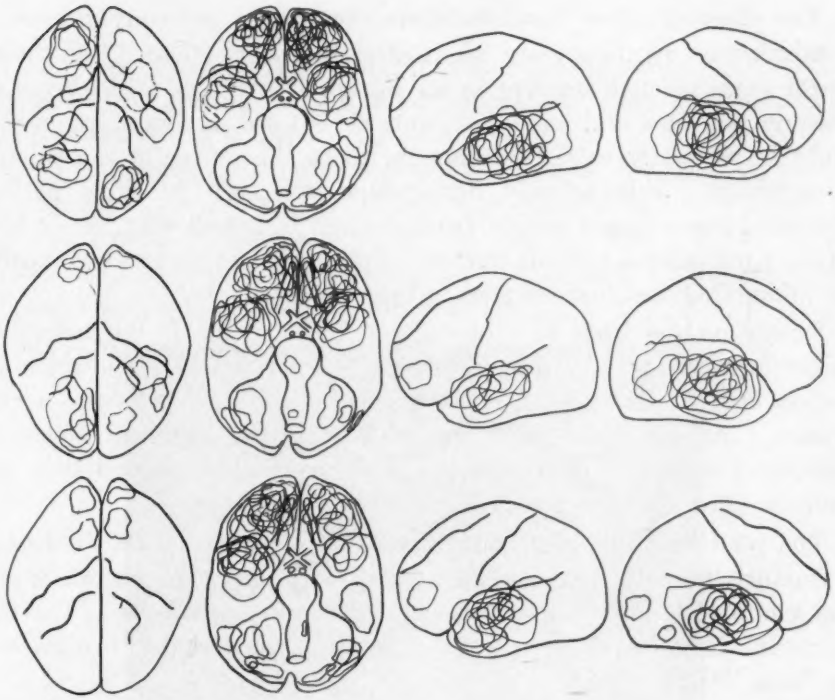

Fig. 5.—Diagrammatic representation of 191 contusions in seventy-two cases. The superior, basal, right, and left lateral views of the brain are shown with the overlying contusions (represented by outline) in three rows. Contusions occurred most frequently on the inferior surfaces of the frontal and temporal lobes.

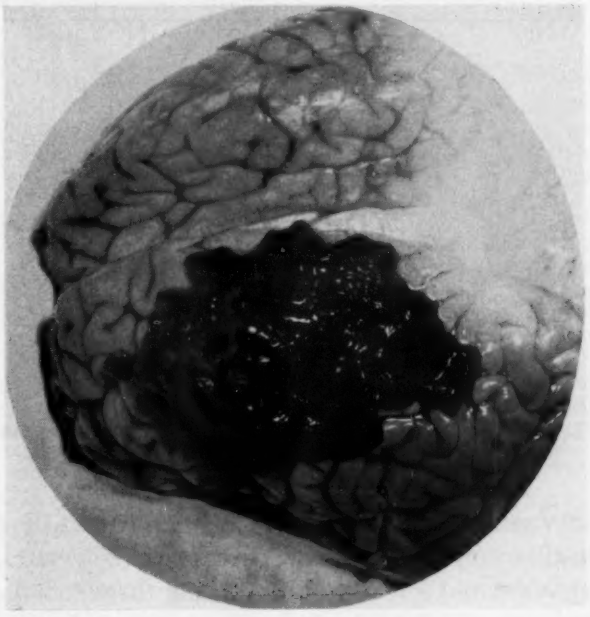

Fig. 6.—An example of one of the acute subdural hematomas encountered. This patient, aged 44 years, was hospitalized after an auto accident. He was unconscious; B. P. 130/90; expired 5 hours later.

The bleeding arose from torn pial vessels on the convexity of the hemispheres. In three cases, an intracerebral clot extended into the subdural space through the tear in the brain. Contusions of the brain surface on the same and on the opposite sides were seen in thirteen cases. Only infrequently were they thought to be the source of the subdural hemorrhage. Subarachnoid hemorrhage was seen in three patients. Petechial hemorrhages were noticed in seven instances, with hemorrhages in the pons and the medulla in four. Epidural bleeding was accompanied by minor subdural hemorrhages in four cases.

Purely on the basis of post-mortem findings, six of the twenty-two might have recovered following operative intervention. The remaining sixteen had profound associated injuries in other parts of the nervous system. Among those with small clots in the subdural space, the associated lesions elsewhere in the brain were marked, and they were thought to be the cause of death.

The position of the clot could not have been guessed on the basis of a fracture line. In eight cases the fracture was on the opposite side from the subdural lesion. There was no fracture in seven cases. The more pertinent facts about these cases of subdural hemorrhage are classified in Table VII.

TABLE VII

SURGICAL (TWENTY-TWO CASES—30 GM. AND OVER) AND NONSURGICAL SUBDURAL HEMORRHAGES (ELEVEN CASES)

	SURGICAL	NONSURGICAL
Side involved		
Right	15	4
Left	7	3
Bilateral	0	4
Fracture		
Same side	7	
Opposite side	8	
Present	15	11
None	7	0
Position of cranium		
Fronto-parieto-temporal	20	10
Basal about chiasm and pons	1	1
Interhemispheric	1	0
Over cerebellar lobe	1	1
Associated pathology		
Contusions and tears	13	Extensive and varied in each instance
Petechial hemorrhage	7	
Larger intracerebral clot	3	
Subarachnoid hemorrhage	3	

The single case of chronic subdural hematoma had been drained through a small trephine opening. At autopsy the cyst cavity was still filled with semisolid and fluid contents. About three-fourths of the hematoma was semisolid. (When the hematoma is mostly semisolid, it should be drained through a small osteoplastic flap rather than through a single or two trephine openings. In the above case, the single trephine opening seemed inadequate.)

EPIDURAL HEMORRHAGE

There were eleven cases of epidural hemorrhage of surgical proportions (about 30 Gm. and over) and an additional four cases of small hemorrhages in the epidural space.

The fronto-parieto-temporal region was the most frequent site among the larger hematomas (Fig. 7). There were eight cases in this group. A bilateral frontal hematoma was seen in one instance. A clot in the parieto-occipital region was present in one case, and a right cerebellar and right occipital localization was found in another (Fig. 8).

Fig. 7.—An example of acute epidural hemorrhage of representative size. This patient, aged 13 years, fell from a bicycle at 5:00 P.M., striking his head on a curb; he walked home, arriving at 6:30. A physician was called and the boy expired at 9:30 P.M.

The source of the hemorrhage was thought to be the middle meningeal artery in nine cases. The dural veins may have contributed to the clot. The frontal hematoma probably arose from venous and anterior meningeal artery bleeding. The clot in the cerebrellar region was of lateral sinus origin.

The larger hematomas were intimately related with fracture except in one case. The fracture was depressed in one instance. It seems that

the position of the fracture is most significant in epidural hemorrhage, making it obligatory to search for the clot in its vicinity. The frontal epidural hematoma without fracture is extremely interesting. Its formation was possibly as follows: A separation of dura and bone may have been initiated by the trauma either by deformation of the cranial vault without accompanying deformation of dural membrane or by actual movement of the dura in the direction of the force when the moving head was suddenly stopped. The initial separation of the dura and bone would cause bleeding into the epidural space. With more bleeding, a further separation of the dura off the bone would ensue, the latter would expose more vessels to add to the bleeding, thus bringing about a vicious circle.

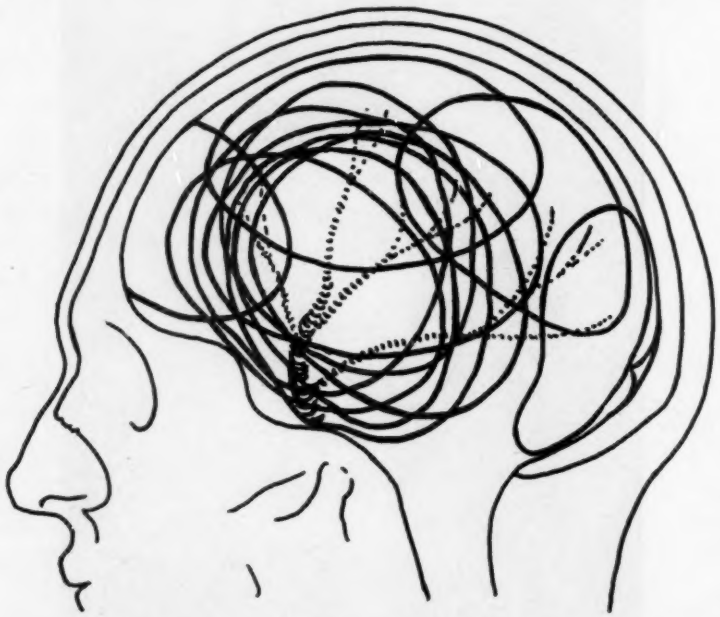

Fig. 8.—Diagrammatic representation of the cases of epidural hemorrhage in this series. Note that the greatest majority occur at the fronto-parieto-temporal region.

Cerebellar epidural hematoma is infrequently diagnosed before death except in puncture wounds of the lateral sinus region. Probably the profound associated lesions of the nervous system mask pure localizing signs. In the case described by Coleman and Thomson, there was a slow onset of stupor and eventual hypotonia and areflexia. A large posterior fossa clot was successfully removed. In selected cases, the site and type of fracture along with clinical evidences of increasing stupor may justify exploration of the posterior fossa for an epidural clot.

In this small group of cases, associated lesions in other parts of the nervous system were frequent. Purely on the basis of post-mortem examination, only two of the eleven cases could have been materially benefited by surgery. It is not surprising that a lucid interval was noted in only two cases.

PETECHIAL HEMORRHAGES

Petechial hemorrhages recognized by gross examination were found to be present in fifty-four cases (Fig. 9). Small hemorrhages were seen in seventeen of the eighteen cases of bullet wounds of the head. Petechial hemorrhages were noted in the pons and in the medulla in a total of twenty-five cases. Twenty of these victims were struck by moving vehicles. Three of the hemorrhages were the result of falls. Six of the group with pontine and medullary lesions showed no fracture of the skull. Four cases of subdural hematoma had associated pontine and medullary lesions. Only six of the twenty-five victims survived the injury, the longest period of survival being thirty-three hours.

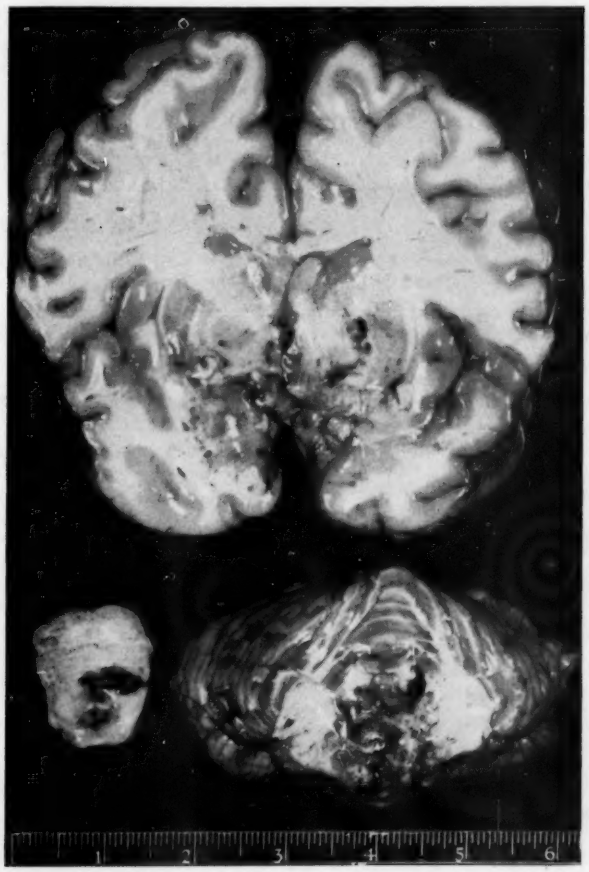

Fig. 9.—An example of unusually severe, diffuse, intracerebral hemorrhages (petechial) involving the brain stem and basal ganglia. This patient was dead on admission to the hospital following an auto accident (associated extensive skull fracture).

Victims Dead on Admission.—An analysis of sixty-one victims dead on admission is shown in Table VIII. Among the sixty-one cases, epidural hemorrhage was noted in 4, subdural hemorrhage in 13, subarachnoid hemorrhage in 18, petechial hemorrhages in 21, contusions in 25, and fracture of the skull in 39 cases. Associated injury elsewhere in the body

TABLE VIII

ANALYSIS OF SIXTY-ONE VICTIMS DEAD ON ADMISSION

Pathology	
Epidural hemorrhage	4
Subdural hemorrhage	13
Subarachnoid hemorrhage	18
Massive intracerebral hemorrhage	0
Petechial hemorrhage	21
Fracture	39
Contusions	25
Associated injuries	
Extremity injury	12
Abdominal injury	2
Chest injury	9
Vertebral column injury	4
Associated injury most important cause of death	9
Age (yr.)	
Under 5	2
5 to 10	1
10 to 20	7
20 to 30	7
30 to 40	8
40 to 50	14
Over 50	22

TABLE IX

ANALYSIS OF THIRTY-NINE CASES WITH NO SKULL FRACTURE

Pathology	
Epidural hemorrhage	1
Subdural hemorrhage	9
Subarachnoid hemorrhage	16
Massive intracerebral hemorrhage	1
Petechial hemorrhage	19
Contusions	13
Associated injuries	
Extremity injury	13
Abdominal injury	3
Chest injury	11
Vertebral column injury	2
Associated injury most important cause of death	9
Age (yr.)	
Under 5	0
5 to 10	0
10 to 20	2
20 to 30	3
30 to 40	9
40 to 50	12
Over 50	13
Duration of life	
Dead on admission	22
2 hr.	3
3 hr.	2
5 hr.	1
10 hr.	1
20 hr.	3
30 hr.	1
2 days	1
4 days	1
5 days	0
Over 5 days	4

was common. The age distribution showed the usual pattern of higher mortality in the older age group.

Cases With No Skull Fracture.—In Table IX the cases with no skull fracture are analyzed. Among thirty-nine such cases, one had epidural hemorrhage and nine showed subdural hemorrhage. In sixteen, there was subarachnoid hemorrhage; in nineteen, petechial hemorrhages; in thirteen, contusions of the brain surface. One case had a rather large intracerebral clot. The age distribution again showed the usual pattern of greater numbers among the older people. The duration of life following trauma has been analyzed for the group. It is noted that twenty-two were dead on admission, and an additional ten died within thirty hours after injury. Amazingly extensive intracranial lesions were frequent.

The question of so-called primary shock causing death may be raised in connection with the cases with no fracture who died soon after injury. Although in a few cases the pathologic changes were slight, intracranial lesions were invariably present in every instance.

Concomitant Injuries.—Associated pathologic lesions other than cerebral were held responsible for deaths in seven of ninety-four cases with fracture of the skull and in nine of thirty-nine cases in which there was no fracture present. In the thirty-nine instances of trauma without fracture, there was associated injury in twenty. Thus, nineteen instances of death occurred without fracture of the skull and without contributive injury, due solely to the intracranial disturbance. The associated lesions in the twenty cases with no skull fracture are given in Table X.

TABLE X

CONCOMITANT INJURIES

INJURY	NUMBER OF CASES
Chest	5
Chest and abdomen	1
Abdomen and extremities	0
Extremity	6
Extremity and chest	4
Abdomen	1
Abdomen, chest, and extremity	1
Fracture vertebral column	2

Clinical Pathologic Correlations.—Seventy-two of the patients in this study reached the hospital after injury. Twenty-two were dead at the time of admission. The remaining hospitalized fifty were distributed among twenty-two hospitals in the Detroit area. The clinical records of these patients were studied in light of subsequent pathologic findings. The length of life, following hospital admission, varied from a few minutes to twelve days. Twenty-six of the group died in twenty-four hours or less after admission. Thus, complete neurologic study was, at times, impossible. In most instances the information contained in the records was incomplete. However, certain findings stand out and are worthy of mention.

Thirty-five patients were unconscious at the time of admission and continued in coma; five were semiconscious and became unconscious; ten showed lucid intervals, either reaching consciousness after being unconscious and lapsing again into stupor (four) or being conscious and then becoming unconscious (six). Among the ten patients with the state of consciousness suggesting a progressive lesion, a subdural or epidural hemorrhage was the cause of death in four cases. (Two of these were operated upon.) In four of the patients there was diffuse brain injury associated with skull fracture; in two, fatty cerebral embolism (Fig. 10) was the cause of death.

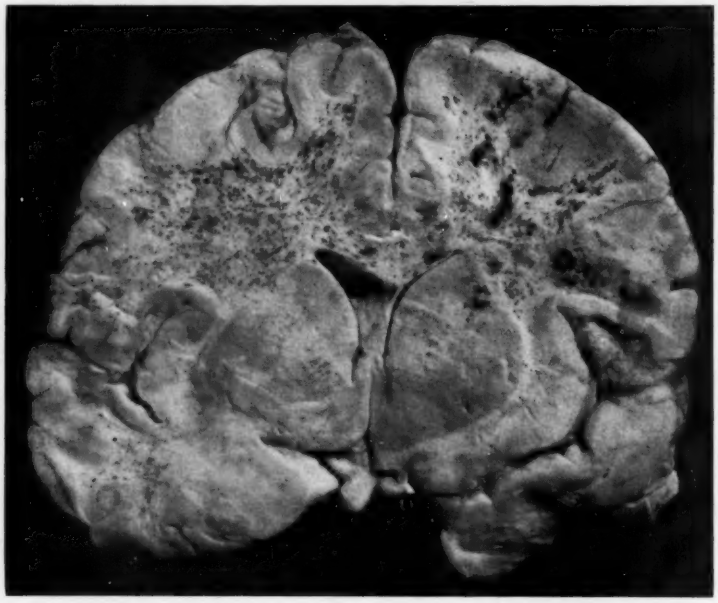

Fig. 10.—An example of cerebral fat emboli complicating head injury. There were fractures of both tibias and a lucid interval of 48 hours. The spinal fluid was slightly bloody with a pressure of 330 mm. of water. The patient was explored for subdural hemorrhage.

Patients were described as being in shock in but two instances. The blood pressure on admission was 84/50 and 60/40, respectively. The blood pressure was low in two other cases (90/0 and 80/54). In one there was associated severe injury to other parts of the body. The greatest majority of those with profound head injury showed no remarkable change in blood pressure and pulse throughout their stays in the hospital.

Hemorrhages from the ears, nose, and mouth were commonly reported in the hospitalized group. Such findings were present in twenty-four of the group of fifty.

Neurologic data were meager, and only gross abnormalities appeared to be reported. Focal signs of paresis, paralysis, or pyramidal tract disturbance were present in thirteen cases. In five instances the signs were bilateral. Seven of those showing focal signs were patients with subdural or epidural hemorrhages. In the hospitalized group, there were seven

subdural, four epidural, and one case of epidural and subdural hemorrhage, a total of twelve. Six of the twelve were operated upon.

Examinations of the pupils were reported in twenty-seven patients. Unequal pupils were present in thirteen instances, five of these in patients with subdural or epidural hemorrhages. One or both pupils were fixed to light in ten instances; in four, the examination was normal.

Correlation of the available information as related to the terminal states of the patients was not suggestive of characteristic clinical patterns associated with characteristic pathologic lesions. Thirteen patients died with temperatures ranging from 105 to 109° F. In five, medullary lesions were present. Respirations were elevated to above 40 per minute in twenty-one cases, four of which showed petechial hemorrhages in the medulla. In five patients, the respirations remained below 20. The most prominent and puzzling feature of the "neurogenic" pattern of death was the tachypnea with or without pulmonary edema.

DISCUSSION

The physical forces producing craniocerebral injuries are varied but may be grouped into the following five general classes: (1) force applied to a relatively fixed head (direct blow); (2) force applied to a nonfixed head which may move by the force (direct blow); (3) force produced by the head in motion coming in contact with a nonmoving or slower moving object (indirect blow); (4) a combination of the preceding circumstances, occurring particularly in auto accidents; (5) in indirect blows, the intracranial contents moving in the direction of the force, may abut against more solid structures, producing bruising of the brain surface (Kocher). Similarly, the "crowding together" of the various portions of the brain itself, because of differences in density, may result in parenchymatous lesions. Contrecoup lesions so common in head injury (Fig. 11) are ascribed to a lag of the brain behind the more rapidly moving cranium, causing the contents of the skull to abut against bone. Another viewpoint worthy of mention is the possible "bouncing back" of the brain when the moving head is suddenly stopped by a nonmoving or slower moving object. Evidence for these conclusions was found in the autopsy material studied.

Contusions and bruises of the brain surface were more frequent on the orbital surfaces of the frontal lobes and at the junction of the frontal and temporal poles of the hemisphere on one or both sides. The higher incidence of bruises in this neighborhood may be due to the many bony irregularities against which the brain rests. The irregular base of the anterior fossa and the sharp edge of the lesser wing of the sphenoid serve as abutments for the brain in motion. Tears and contusions may ensue in these areas following sudden arrest of the brain. When the direction of the blow causes the intracranial contents to move posteriorly, the tentorium cerebelli may accomplish much in protecting the brain. Contusions of the more posterior portions of the brain were infrequent, we believe, because of the "buffer" role of the tentorium. In the dog,

the osseous tentorium has no "give" as is the case in the human. Therefore, it is reasonable to expect that a higher incidence of injury would obtain in the occipital regions in the animal. In the human being, since a majority of the contusions occur on the anterior third of the brain surface, it is no wonder that most of the cases of subdural hemorrhage occur in the fronto-parieto-temporal regions.

The occurrence of multiple petechial hemorrhages associated with cranial trauma has been frequently noted and commented upon (Cassasa, Vance, Martland, and Beling). Aside from those caused by emboli (fat embolism, endocarditis, etc.), petechial hemorrhages are probably brought about by a combination of trauma and pathophysiologic changes. The "crowding together" of the various portions of the brain may cause parenchymatous damage due to "squashing." The resultant localized area of damage interferes with the normal nutrition and capillary-tissue

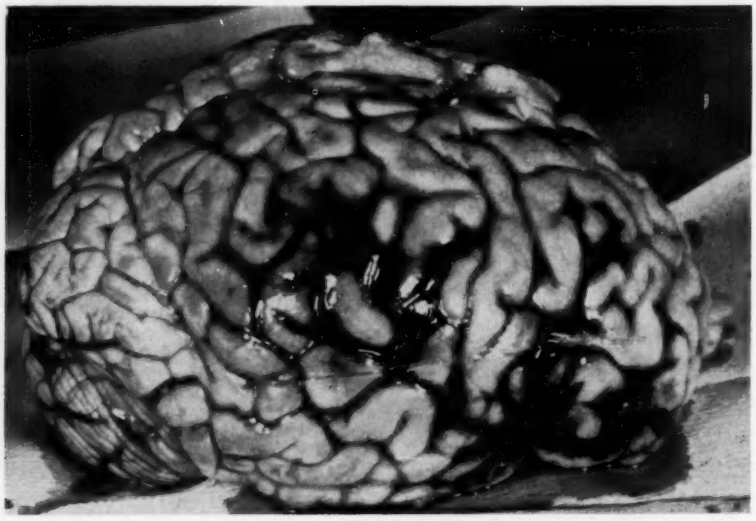

Fig. 11.—An example of contrecoup injury to the cortex opposite the site of a depressed, fractured skull.

exchange of the region, causing stasis, necrosis, and hemorrhage by diapedesis. It is well known that petechial hemorrhages may occur without trauma (usually preterminal). In such cases due to alteration in blood supply of the brain, a vascular stasis with anoxia may cause areas of necrosis eventuating in small hemorrhages by diapedesis and vessel wall damage. Of interest is the finding of petechial hemorrhages in the spinal cord in experimental head injury (Jakob, Denny-Brown).

Of the total group of 151 cases studied, there were twenty-two instances of acute subdural hematoma, eleven cases of epidural hemorrhage, and one case of chronic subdural hematoma, representing in their total, 21.5 per cent of the entire group. These thirty-four lesions were of sufficient size to classify as operable in type. Vance found that 26.2 per cent of the patients of 507 autopsied cases died as a result of either

subdural or epidural hemorrhage. Munro reported these types of surgical lesions in 20.8 per cent of 1,203 cases of head injury. One must conclude that hemorrhage producing a cerebral mass lesion is of frequent occurrence following trauma. When unassociated with profound intracerebral injury, the results of surgical treatment are highly satisfactory. Accompanying bruising of the brain, petechial hemorrhages or both occurred frequently as previously noted. This fact is an important consideration in management.

Analysis of this group showed that while fracture of the skull was present and was on the side of the lesion in all of those patients with epidural hemorrhage, fracture was commonly absent in the subdural hematoma class. In eight instances it was found that the subdural hematoma was on the opposite side to the fracture. While roentgen studies would be of assistance in localizing the epidural hemorrhage on the basis of the site of fracture, this would not hold in the subdural hematoma group.

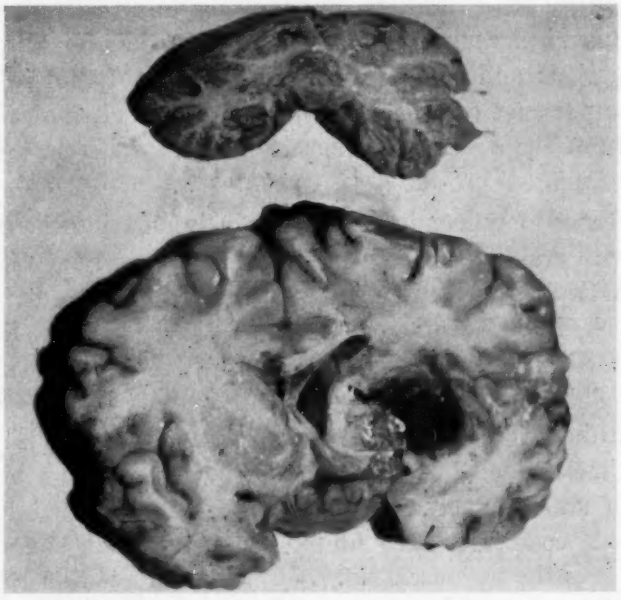

Fig. 12.—An example of traumatic intracerebral hemorrhage of the massive type. The patient, aged 23 years, was struck by an automobile, and lived 8 hours; conjugate deviation of eyes to side opposite lesion; had cycles of relaxation followed by clonic movements of all extremities which changed into "a definite extensor tonic convulsion." Bilateral pyramidal signs were present.

Massive intracerebral clot was present in one case in this review (Fig. 12). It was in the temporosphenoidal lobe. Such localization is the commonest of subcortical clots of larger size. They occasionally accompany middle meningeal hemorrhage (Apfelbach). The clinical studies of Courville and Blomquist and Pilcher suggest that massive intracerebral clots occur more frequently than seen in this study, and such lesions may escape early recognition. Later they may cause symptoms leading to their exploration. However, most surgical lesions of the intracranial

contents caused by trauma are found on the surface of the brain and intracerebral clots of surgical size are rare.

The significance of the presence or absence of a fracture of the skull in assessing the degree of cerebral injury is well brought out by this review.

The presence of a fracture has been repeatedly considered of major prognostic significance. It has been used as a criterion as to whether a patient should be hospitalized and for how long. In all probability it is true that a fracture of the skull is a rough index of the severity of the trauma. Associated damage to the intracranial contents is more common among the patients with fracture than those without bone injury. However, the absence of a fracture does not rule out severe and at times fatal intracranial injury. In 151 examinations, there were thirty-nine with no fracture of the skull. Of the thirty-nine cases, there was no associated injury in nineteen. Thus, these nineteen patients died solely of traumatic intracranial lesions. Particularly with the indirect type of injury to the head, the movement of the brain in the cranial cavity may produce contusions and tears or may result in profound intracellular damage. The presence or absence of a fractured skull as a criterion for the evaluation of the degree of cerebral injury would seem to be a loose standard.

The importance of concomitant injuries in influencing the outcome of the patient with cranial trauma was shown in this study. With indirect blows and particularly with injuries of great violence, not only may the head be struck, but also other portions of the body as well. In this study, associated pathologic lesions elsewhere than in the head were believed responsible for death in seven of ninety-four patients with skull fracture and nine of thirty-nine patients in whom no fracture was present. Early knowledge of the presence of such secondary injuries appears to be of major importance. The condition which mainly obscures the diagnosis of commonly encountered chest, vertebral, abdominal, and pelvic injuries is the unconsciousness of the patient with a centering of interest to the head.

Although this is primarily a discussion of gross findings in a series of necropsied cases, it would not be complete without a few words concerning increased intracranial pressure. Increased intracranial pressure has been attributed to edema of the brain, hemorrhage of intracranial contents, and increased intracranial blood volume due to trauma (Shapiro and Jackson). That hemorrhage into the intracranial contents can and does cause increased intracranial pressure is accepted. This is brought about by an actual increase in the volume of the intracranial contents by the escape of blood, or the bleeding, particularly into the subarachnoid spaces, may increase the osmotic pressure of the spinal fluid (Howe, Parker and Lehman) by increasing its protein content. Increased os-

motic pressure would cause transfer of tissue fluids into the subarachnoid bed. A combination of the above is probably operative in a great many of the cases.

Traumatic edema of the brain was attributed by Cannon to increased osmotic pressure of brain tissue caused by extravasation, contusions, small thrombi, and necrosis. Courtney suggested that transudation of fluid about and into areas of laceration and bruises is the cause of brain edema. He felt that the process is similar to the edema about an inflammatory lesion elsewhere in the body.

Because the microscopic appearance of edema (increased tissue spaces between cells with many dead and dying cells) occurs not only about actual lesions but also in distant portions of the brain, other explanations have been sought for the generalized process. Vasomotor paralysis of cerebral vessels by trauma (Courtney) with subsequent venous stasis and tissue waterlogging, due to increased permeability of the capillaries, has been considered a possibility (Ricker). An initial localized edema may compress the brain, altering its nutrition; thus, a localized edema may be enhanced by anoxemia and anoxia and eventuate in generalized edema of the brain due to venous stasis, increased capillary permeability, and eventual tissue waterlogging (Schaller). Probably more than one factor is in operation. Increased osmotic pressure of the brain and spinal fluid with edema in conjunction with the lack of proper oxygen supply may be the basis for the generalized swelling of the brain in the absence of extensive intracranial hemorrhage.

Other explanations of increased intracranial pressure without severe hemorrhage are irritation and stimulation of the choroid plexus (Rand and Courville), with increased cerebrospinal fluid formation or the lowering of the rate of absorption of the spinal fluid due to venous stasis and increased venous pressure well above that of the cerebrospinal fluid (Jorns, Haussler, and others). In this connection, Weed felt that increased protein content in the cerebrospinal fluid due to blood retarded its absorption. It has long been suggested that there is traumatic internal hydrocephalus in many cases of fatal injury to the head. Jackson, and Shapiro and Jackson, in post-mortem studies, have recently reemphasized the presence of increased intraventricular fluid and internal hydrocephalus in cases of head injury.

Among others, Haussler and Jorns distinguished between swelling and edema of the brain. Recently, Pilcher, Shapiro, and Jackson studied the water content of traumatized brains. They did not find any increase in water content. This suggested that the brain swelling was not due to edema. Shapiro and Jackson found an increase of extra- and intravascular blood content of the brain. This factor, as well as increased intraventricular fluid, was considered the basis for brain swelling by these authors. The cause for the swelling in cases of minimal hemorrhages is obscure. To what extent post-mortem findings of the

fluid content represent the true premortem conditions in the brain is also not clear. Alexander and Looney have raised many interesting questions in this connection. They reported that the amount of postmortem water content of the brain was not a true index of edema or swelling.

That increased intracranial pressure due to trauma is a clinical entity is universally accepted. That some brains look swollen at autopsy, even though the subarachnoid spaces are obliterated (thus making the brain surface appear dry), cannot be denied. In occasional instances we have observed large amounts of fluid in the subarachnoid and subdural spaces. An acceptable viewpoint is one which does not deny the occurrence of edema and yet does accept that it may be present in some cases, due to the time of death, to treatment prior to death, and to a different set of physicochemical factors operating in a given case.

Although the pathologic findings in some of the cases in this series were minimal, all showed gross abnormalities. Death from so-called concussion* was not seen in this series. Examination of the clinical material available showed also that the occurrence of shock was infrequent if not unusual in uncomplicated cases of head injury. Increasing pulse rate with lowering blood pressure and other characteristic signs of shock were reported in only two instances among the clinically observed group. The physiologic state present in those patients who died instantly or immediately following trauma can only be conjectured upon. Of twenty-two victims who were dead on admission to the hospital, all but two showed severe pathologic damage to the brain and fractures of the skull. There were three instances of subdural hematoma.

SUMMARY

1. In practically every instance of fatal head injury there is a combination of pathologic processes. For example, although the chief lesion may be an epidural hemorrhage, petechial hemorrhages and cerebral bruises frequently coexist.

2. There is great variation in the extent and severity of brain lesions in the fatal cases. Among some, few pathologic lesions were noted to explain the cause of death. However, in every case, gross lesions were found.

3. A massive intracranial hemorrhage due to trauma is usually on the surface of the brain and may be amenable to surgical treatment. Large intracerebral clots are rare.

4. In epidural hemorrhage, exploration about a fracture line seems justifiable. In subdural hemorrhage, a fracture line is of little value in localization, often being opposite to the side of the subdural hemorrhage.

*The term concussion is used in a most elastic manner by different authors. As understood in this paper, concussion is characterized by an unconscious state after head injury unassociated with macroscopic or microscopic lesions of the brain.

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A CASE OF EPIDERMOID TUMOR OF THE SPINAL CORD

REVIEW OF LITERATURE OF SPINAL EPIDERMOIDS AND DERMOIDS

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INCLUSION cysts developing in relation to the spinal cord and its meninges are rare in the experience of most neurologists and neurosurgeons. The standard textbooks make scant reference to these tumors, but in the periodic literature one finds a sufficient number of case reports to establish them as a not uncommon clinico-pathologic entity. On the basis of gross and histologic characteristics three distinct types are recognized: (1) the epidermoid or cholesteatoma, containing only epidermal tissue and its debris; (2) the dermoid, containing, in addition, dermoid structures and derivatives; and (3) the teratoma, containing tissues derived from two or more germinal layers. The case reported here is believed to be an example of the first type.

REPORT OF A CASE

History.—W. M. (A-55912), a 25-year-old white male, referred to Duke Hospital with a tentative diagnosis of "spinal cord tumor," was admitted to the neurologic service, Feb. 12, 1941. He complained of low back pain and numbness, tingling and stiffness in his legs of five months' duration. His general health had always been excellent. There was no history of injury. Since early childhood he had had what he called "growing pains" in the thighs, occurring at night after strenuous work or exercise. He also described infrequent attacks of a rather sharp pain in his lower thoracic spine radiating toward the left scapula, brought on by jarring or suddenly turning the body to either side. In October, 1940, or about five months before admission, he began to notice on going to bed a dull, poorly localized ache in the lower part of the back which would keep him awake for several hours, together with numbness and tingling in the anterior thighs, first on the left and later bilateral. He had sometimes awakened during the night with uncertainty as to the position of his feet in the bed. At first he did not notice these symptoms during the day, but gradually they became more constant. The numbness and tingling spread downward to the feet. About four months before admission he began to notice slight hesitancy in initiating urination. Stiffness of the legs developed gradually, and his gait became unsteady. Following a lumbar puncture on February 7, he noticed for the first time slight weakness of his legs, causing increased difficulty in walking. He had lost twenty pounds in weight.

Examination.—Physical examination revealed an undernourished young man with poor muscular development, who did not appear acutely ill. A general glandular enlargement was present, the nodes being hard and nontender. Examination of the back with the patient standing disclosed obliteration of the normal lumbar curvature and a moderate scoliosis, with convexity to the right, involving the lower thoracic and lumbar spine. There was no localized deformity or tenderness of the spine.

Neurologic examination revealed no abnormality in the cranial nerves or upper extremities. The muscles of the back and abdominal wall functioned normally.

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Both legs were slightly spastic, but strength appeared to be normal in all muscle groups. There was no atrophy, and fasciculations were not seen. Sensory examination revealed a fairly sharp level at the upper border of the eleventh thoracic dermatome bilaterally, below which there was anesthesia and marked hypalgesia extending down to include the third lumbar dermatome. From the fourth lumbar to the second sacral dermatome the hypalgesia was less marked, and light touch was appreciated. Over the buttocks the sensory loss was not symmetrical: on the right there was moderate hypesthesia and hypalgesia, whereas on the left light touch was not appreciated at all, but pinprick produced an intensely painful sensation which was poorly localized. Position sense was markedly impaired in the toes bilaterally, and vibratory sense was absent below the knees. In placing the heel on the knee he showed slight sensory ataxia. His station was unsteady with eyes closed, and his gait was moderately ataxic. The abdominal reflexes were present except for the left upper, which could not be obtained. The knee and ankle jerks were hyperactive bilaterally, and there was sustained ankle clonus on the left. The plantar responses were extensor in type.

Examinations of the urine and blood showed no abnormality, and the blood Wassermann was negative. The spinal fluid was clear and colorless. The initial pressure was 110 mm. of water. Manometric tests performed according to the standardized technique of Grant and Cone[1] suggested partial subarachnoid block. The first specimen of fluid removed gave a strongly positive reaction for protein (Pandy test), whereas the final specimen gave a negative reaction. The fluid contained no cells. The Wassermann and colloidal mastic tests were negative.

Roentgenograms of the spine showed scoliosis to the right starting at the tenth thoracic vertebra and extending to the fourth lumbar, with rotation of the bodies of the lumbar vertebrae to the right. There was partial spina bifida of the first sacral segment with the right lamina lying about 8 mm. beneath the left lamina. The lumbosacral articulations could not be distinctly seen. After injection of 2 c.c. of iodized oil (Lipiodol) into the cisterna magna, fluoroscopy and films revealed a marked delay in the passage of the oil at the level of the eleventh thoracic vertebra, the oil passing in a thin stream to the right of an apparent obstruction.

Following lumbar puncture the patient complained of a slight increase in his original symptoms, and examination revealed more pronounced sensory loss over the segments previously involved. A tentative diagnosis of intramedullary tumor at the level of the eleventh thoracic vetebra was made, and he was transferred to the neurosurgical service.

Operation.—A midline laminectomy incision was made over the lower thoracic spines. The spinous process and laminal arch of the eleventh thoracic vertebra were resected. On opening the dura an extensive soft arachnoiditis was noted. Just below the level of the dural incision a rounded, yellow mass could be seen, apparently lying within the conus medullaris. The spinous process and laminal arch of the twelfth thoracic vertebra were then resected, and the laminal arch of the first lumbar vertebra was beveled slightly, giving a dural exposure about 7 cm. in length. On extending the dural incision a very striking picture was seen (Fig. 1). A well-demarcated, yellowish-white tumor mass filled the conus medullaris, coming to the surface on the left dorsal aspect of the cord, covered only by a thin layer of pia-arachnoid membrane. The tumor measured 3 cm. in length and 1.5 cm. in width and depth, the upper pole being at about the level of the third or fourth lumbar segment of the cord. It was slightly nodular. The entire mass was gently dissected out of its bed in the cord, and no clearly defined membrane could be seen surrounding it. It appeared to be a cholesteatoma. When dissecton was completed, there was no evidence of a cyst wall or of any tumor tissue remaining in the pocket.

Postoperative Course.—Immediately after operation the patient had complete paralysis and anesthesia of both lower extremities and urinary retention, requir-

ing daily catheterization. Within the first week he showed slight return of motor function in the right leg. On the eleventh postoperative day he began to void spontaneously. He continued to improve slowly, regaining some function in all muscle groups of the right leg and ability to move the left toes. There was also some return of sensation. He was discharged on the twenty-eighth postoperative day. He returned to the outpatient clinic approximately six months after operation, reporting slight improvement during the first two months but none since then.

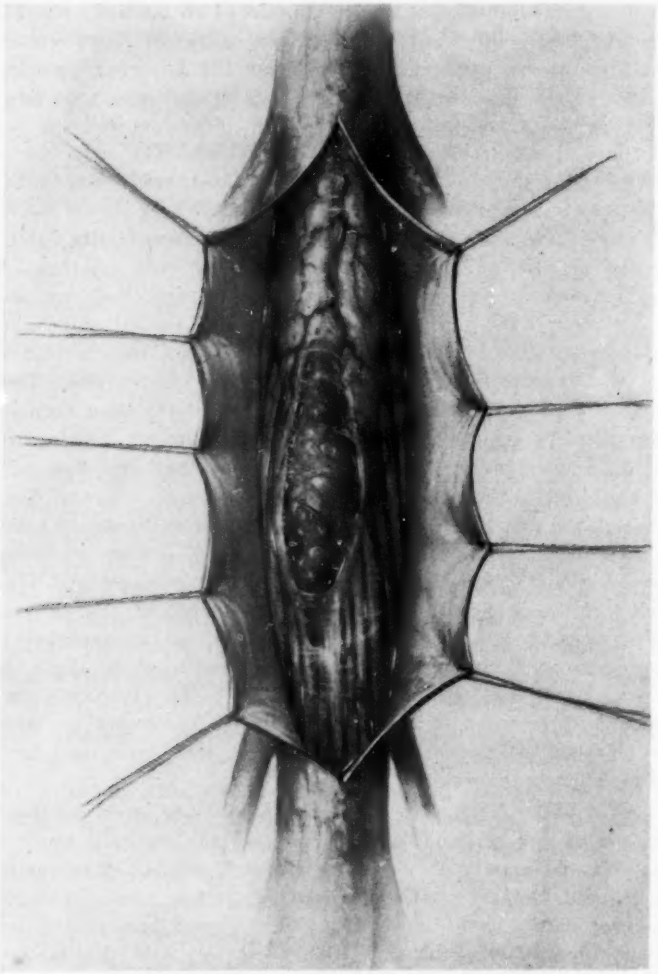

Fig. 1.—Drawing of operative field after retraction of the dura. The main body of the tumor lies in the conus, covered only by a thin membrane of pia-arachnoid.

He was unable to walk, except with crutches. He complained of hesitant micturition and complete impotence. On examination he was found to have a spastic paraplegia with little useful function in his legs and marked reduction in all forms of sensation below the tenth thoracic dermatome. His condition appeared to be stationary, and no further change was anticipated. His physician reports that he has subsequently returned to work at a sedentary job.

Pathologic Study.—Grossly the specimen consisted of several small pieces of soft, friable, cheesy material of a yellowish color, in which small lumps of a slightly firmer consistency could be felt. No encapsulating membrane could be

seen grossly and no hairs were present. Microscopic study of several serial sections taken from one of the larger fragments, stained with hematoxylin and eosin, showed what appeared to be a multiloculated cyst with numerous invaginations and outpouchings of its wall (Fig. 2). The cyst wall appeared as a crumpled purselike membrane composed of two or more layers of well-preserved basal cells. Inside this basement membrane, and closely attached to it, were several layers of desquamating squamous cells which had lost their nuclei. These merged with an amorphous, vacuolated, necrotic substance in which the only recognizable cells were red blood cells, apparently from operative bleeding. Outside the membrane there was no supporting tissue, only scattered bits of tissue which, when stained with Mallory's phosphotungstic acid hematoxylin, appeared to be composed of interlacing fibers and large nucleated cells resembling nerve cells. It was thought that these might represent small pieces of spinal cord substance which had adhered to the basement membrane during removal of the tumor. No glands or hair follicles were seen in any of the sections. There was no evidence of malignant change. In a frozen section stained by Herxheimer's scarlet red the amorphous substance was found to contain numerous globules of fat. With the polarizing miscroscope, doubly refractile crystals characteristic of cholesterol were identified (Fig. 3). The pathologic diagnosis was "epidermoid of spinal cord."

DISCUSSION OF CASE

It is worth noting that this patient had had symptoms referable to his lesion since early in childhood. This fact, together with the finding of spina bifida of the first sacral segment, should have raised the suspicion of a congenital lesion. Spina bifida of the sacral segments is not an unusual finding in patients without neurologic complaints, but in this case the fact that the corresponding segment of the cord was involved by the tumor makes it highly probable that the two conditions were embryologically related. The sensory level was at the eleventh thoracic dermatome, and the upper pole of the tumor was at the level of the eleventh thoracic vertebra or at the third or fourth lumbar segment of the cord. The cutaneous sensory loss between the eleventh thoracic and third lumbar segments, therefore, must have been due either to compression of the nerve roots or to the arachnoiditis which was present. The tumor occupied a cleft between the posterior columns of the cord, lying slightly to the left of the midline. Practically its entire dorsal surface was exposed, being covered only by the pia-arachnoid. It must, therefore, be classified as subpial rather than intramedullary. Histologically this tumor was quite remarkable in that the basement membrane did not form a definite cyst wall but was folded up within the substance of the tumor; in places it was impossible to say whether the desquamating epithelium was on the inside or on the outside of the membrane. This suggests that the membrane was actively proliferating but did not have room to expand, with the result that it became folded on itself, entrapping between its folds desquamating squamous cells on one side and spinal cord tissue on the other. If fragments of spinal cord substance were removed with the tumor, as the sections suggest, this would adequately explain the postoperative development of paraplegia and the unsatisfactory surgical result.

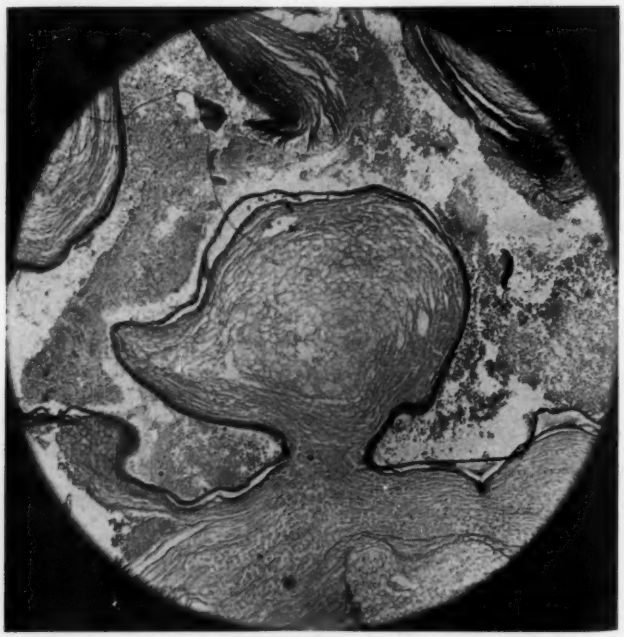

Fig. 2*A*.—Photomicrograph showing low-power view of a portion of the tumor. The pedunculated nodule in the center of the field is covered by basement membrane, and its center consists of degenerative squamous cells and cellular debris. The material outside the membrane consists mainly of red blood cells, thought to be artifact resulting from bleeding at operation. (Hematoxylin and eosin stain, ×43.)

Fig. 2*B*.—Photomicrograph showing stratified squamous epithelium cut in tangential section. The blood-filled spaces lined by basal cells represent small invaginations of the cyst wall. (Hematoxylin and eosin stain, ×160.)

REVIEW OF LITERATURE

The reported cases of dermoid and epidermoid tumors of the vertebral canal have been reviewed by Critchley and Ferguson,[2] Gross,[3] Bradford,[4] and most recently by Boldrey and Elvidge.[5*] The cases collected by Boldrey and Elvidge, in 1939, number thirty-seven, to which they added three of their own. These authors state that in all instances they

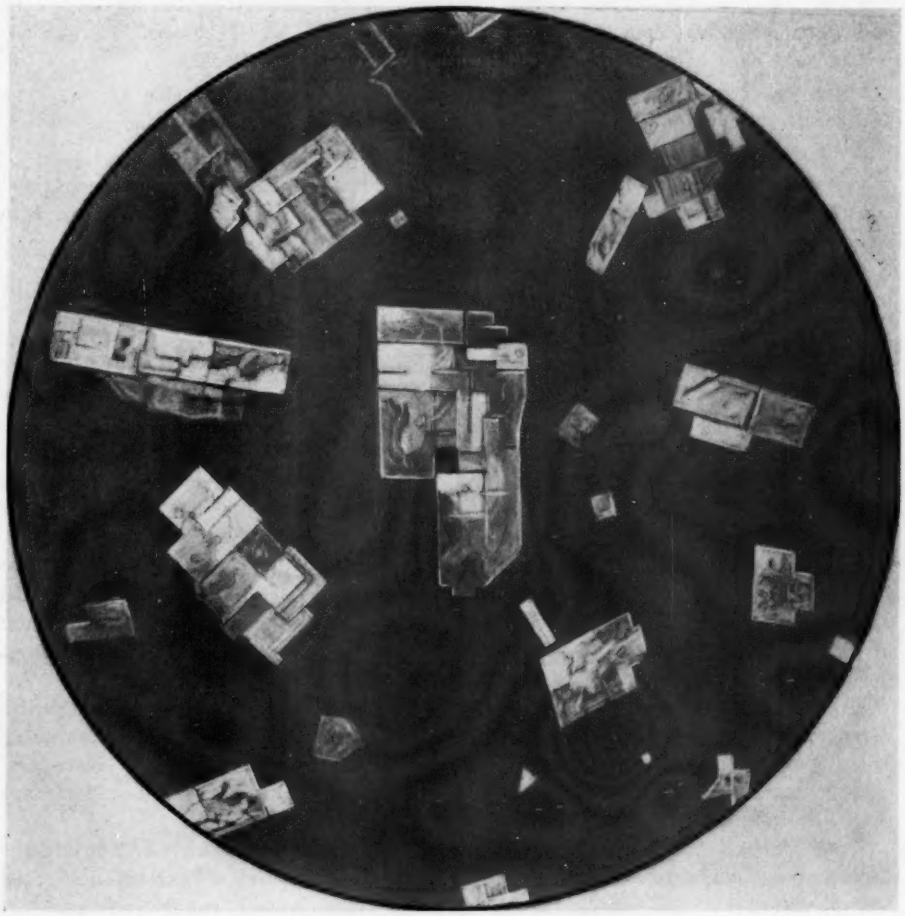

Fig. 3.—Camera lucida drawing of doubly refractile cholesterol crystals, seen with the polarizing microscope, in a piece of formalin-fixed tissue from the tumor.

have assumed the accuracy of the original pathologic diagnosis. I have reviewed as much of this literature as is available and am unable to accept the following cases as either dermoids or epidermoids, for the reasons stated. (The case numbers correspond with the enumeration in the authors' lists.)

CASE 1 (Eppinger).—The only available reference to this case is in the review by Critchley and Ferguson,[2] and the data given are insufficient to make a diagnosis.

*A more recent review is to be published by Bagley and Arnold, who have kindly permitted me to read their manuscript.

CASE 6 (Ivanoff).—The original article is unavailable. From the facts given in various reviews, this was apparently an anencephalic monster which died at birth and was found to have a malformation of the entire cerebrospinal axis. It cannot properly be classified as a tumor or cyst.

CASE 7 (Raymond, Alquier, and Courtellemont[6]).—In this case the principal lesion, a frontal lobe dermoid, was adequately proved. The multiple fatty lesions in the spinal meninges were apparently not studied microscopically but were assumed to be dermoids because of gross similarity to the cerebral lesion.

CASE 10 (Frick[7]).—This tumor contained bone marrow with myeloid cells and giant cells, calcium, connective tissue, hair, and blood vessels. It was reported as a case of teratoma and has been so accepted by Hosoi.[8]

CASE 13 (Elsberg[9]).—There is no pathologic description of this tumor. The author cites the case as one of questionable dermoid cyst, but the accompanying photomicrograph is labeled "gliomatous (?) cyst."

CASE 33 (Naffziger and Jones, Case 3[10]).—This tumor is said to have contained connective tissue, calcium, and a substance resembling cartilage. I am inclined to regard it as a teratoma.

The following cases, either omitted or published subsequently, should be added to the collection of Boldrey and Elvidge.

Craig and Mitchell,[11] in 1931, reported an 8-year-old boy with a history of intermittent back pain, nocturnal incontinence, and weakness of legs for three years. There was a dimple in the skin at the level of the fourth lumbar spinous process. Neurologic findings suggested tumor of cauda equina. At operation the dura was joined to the laminal arch of the fourth lumbar vertebra by a fibrous band. A subdural tumor compressed the conus and cauda equina. Diagnosis: Cholesteatoma. The patient has improved markedly.

Bouchut, Dechaume, and Michailidis reported, in 1932, a case reviewed by Bradford.[4] It was that of a 71-year-old man with history dating back fifteen years, who came to autopsy and was found to have an intramedullary epidermoid of the conus medullaris. In addition there was dysembryoplasia of the adjacent portions of the cord and syringomyelic cavities.

Walker and Bucy,[12] in 1934, published a discussion of seven cases of congenital dermal sinus. The authors cite one case, originally reported by W. and N. Sharpe, in which such a sinus, chronically infected, was associated with an intradural cyst containing caseous material and hair. Although no pathologic report was given, the authors concluded that this was a dermoid.

Bradford[4] reported a case in 1938. This 3-year-old boy had had symptoms for one year, and examination disclosed a flaccid paraparesis, perianal analgesia, and a palpable defect in the sacral laminae. The lumbar canal was markedly dilated. Operation consisted of incision and evacuation of an intramedullary cyst of the conus medullaris. The cyst wall was composed of simple, stratified, squamous epithelium. A mural nodule, however, contained hair follicles and sebaceous glands in addition to epidermis. The diagnosis was "dermoid cyst." The patient improved somewhat.

Masson,[13] in 1938, reported a 38-year-old man with recurrent attacks of back pain and progressive neurologic disturbances for 17 years. There was spastic paraparesis with the sensory level at the ninth thoracic dermatome. Laminectomy revealed a "pearly tumor" at the eighth to ninth thoracic vertebra, lying between the pia and arachnoid on the dorsal surface of the cord. It contained hairs, and the pathologic diagnosis was "dermoid cyst." The patient was relieved of pain but the paraparesis became worse.

Walker and Moore[14] published an article in 1939. Although reported as a case of teratoid tumor, this appears to have been an instance of infected dermal sinus

and subdural dermoid cyst, similar to the case of Walker and Bucy described previously. Following an acute febrile illness diagnosed "meningitis," a 3-year-old boy developed rapidly increasing weakness of the legs. Examination disclosed spastic paraplegia and analgesia below the fifth thoracic dermatome. At the level of the ninth thoracic spinous process there was a cutaneous dimple from which hairs protruded. At operation a dermal sinus was traced from the dimple down to the dura, where it ended in a mass of distorted dermal structures and infected granulation tissue. Beneath the dura there was a large cyst compressing the cord to a mere ribbon. It contained desquamated epithelium, hairs, and debris. Its wall was composed partly of epithelium and partly of fibrous granulation tissue. Death occurred postoperatively.

Verbiest,[15] in 1939, reported a 65-year-old man who had had mild symptoms of spinal cord disease since the age of 12. All forms of sensation were impaired below the twelfth thoracic dermatome. The right leg was spastic, the left flaccid and atrophied. Lipiodol showed a block at the level of the twelfth thoracic vertebra. Laminectomy revealed chronic arachnoiditis and an intramedullary cyst. This contained gruellike material which by chemical analysis was found to consist of cholesterol, fat, and fatty acids. The capsule was composed of stratified squamous epithelium. Diagnosis: Epidermoid cyst. The patient developed postoperative sterile meningitis lasting four weeks. His condition was not improved by operation.

Bagley and Arnold[16] reported, in 1940, a 9-year-old boy with symptoms which brought him to an orthopedist, who found flexion deformities of the knees and hips, backward tilting of the pelvis, paravertebral tenderness, and muscle spasm. The only abnormal neurologic finding was a hyperactive right knee jerk. Lumbar laminectomy revealed a markedly tense dura, incision of which released a large amount of soapy material in which cholesterol crystals were identified. An encapsulating membrane was dissected away from the nerve roots, and microscopic study of this showed stratified epithelium beneath which there was a well-defined layer of connective tissue. Many hairs were found. The diagnosis was dermoid cyst and the patient was relieved of all symptoms.

This revision of Boldrey and Elvidge's collection brings to forty-two the number of reported cases in which critical analysis of the evidence justifies the diagnosis of dermoid or epidermoid tumor of the vertebral canal; an additional case is reported. In this review the dermoids and epidermoids have been grouped together, and this has been the tendency of all recent authors. The teratomas, or tumors containing derivatives of more than one germinal layer, are usually treated as a separate group and have been omitted. These tumors have been reviewed by Hosoi[8] and more recently by Masten.[17] To date fourteen cases have been reported.* Cases of congenital dermal sinus, as discussed by Walker and Bucy,[12] have also been omitted except for those cases in which a definite dermoid cyst within the spinal canal has been demonstrated.

COMMENT

In the foregoing review no distinction has been made between the dermoids and the epidermoids, and it has been the custom of recent authors to group these together under the inclusive term "dermoids." While

*Since the writing of this paper, L. A. French and W. T. Peyton (Arch. Neurol. & Psychiat. 47: 737-751, 1942) have reported two additional cases of teratoma and one of epidermoid tumor.

this grouping is perhaps justifiable for purposes of historical review, considering that the published data often are insufficient to permit an accurate pathologic diagnosis, I feel that the clinical features and growth characteristics of the two types are sufficiently different to render separate discussion advisable. The following discussion is based upon an analysis of the clinical, operative, and pathologic findings in the forty-two cases comprising my revised collection of cases, and in the one reported here. Wherever possible, reference has been made to the original publications for details not mentioned in the reviews.

In differentiating between dermoids and epidermoids the criteria of Ewing[18] have been employed. He states that the simple dermoid consists of epidermis, dermis, and dermal derivatives, such as hair, glands, and sometimes teeth. It usually appears in the form of a cyst, commonly originating by the inclusion of a portion of ectoderm during the closure of embryonal fissures, or at the point of union between ectodermal and other structures. In the epidermoid, also known as cholesteatoma, definite dermal structures are wanting. This is a tumor composed of lamellated, waxy, or scaly material enclosed in a wall of stratified, squamous epithelium. It is regularly connected with the meninges. In both types disintegration of the epidermal slough gives rise to cholesterol crystals, which are found within the cyst.

Epidermoids.—Eighteen cases in the series are probably epidermoids; in two others the diagnosis of epidermoid is questionable but cannot be disproved, so they are included. The onset of symptoms occurred in the first decade in two cases, in the second in seven cases, in the third in four cases, in the fourth in three cases, and beyond the age of 40 in three cases. In one case the tumor was asymptomatic. The usual clinical course is that of any benign tumor of the spinal cord, except that paraplegia tends to develop more slowly. In two cases, however, the symptoms were intermittent and of rapid onset. In the case reported by Critchley and Ferguson[2] there was a history of cerebrospinal meningitis in infancy with complete recovery, transient paraplegia at 7 years of age, and rapid recurrence of paraplegia following an attack of influenza at the age of 15; the epidermoid was intradural but extramedullary at the seventh to eighth thoracic segments, and there was no evidence of encapsulation. Michelson's patient[19] had a history of paraplegia lasting six weeks after administration of a spinal anesthetic, followed three years later by a spontaneous episode suggestive of acute transverse myelitis; an extramedullary epidermoid lay on the posterior surface of the cord at the ninth thoracic vertebra. The observations and theories of Verbiest[15] offer a possible explanation for the occurrence of these acute and transient episodes. In his case, abstracted above, chronic arachnoiditis was found at the site of a subpial epidermoid, and after operation the patient developed a sterile meningitis lasting four weeks. The author suggested that this was due to liberation of fatty acids from the necrotic contents of the cysts, which

he demonstrated by chemical analysis. He produced, furthermore, sterile meningitis experimentally by injecting fatty acids into the subarachnoid space of a dog. He did not go so far as to suggest that transverse myelitis might be caused by chemical irritants elaborated by the tumor, but in the light of the above mentioned cases this possibility is to be considered. In our own case it furnishes an alternative explanation for the postoperative paraplegia.

Spina bifida is not a frequent finding in the cases of epidermoid tumor, being reported in only two. One of these is the case reported here, in which the first sacral laminae were unfused. Since the tumor involved the corresponding segment of the cord, it seems likely that this represents an embryologic defect common to the spinal cord and vertebral column rather than a chance association. It is quite possible that the incidence of spina bifida would be higher if routine x-rays had been taken. In no case has a communicating dermal sinus been reported.

Epidermoids have been found at all levels of the spinal canal as high as the second thoracic vertebra; none has been reported in the cervical region. All have been intradural, with one exception, the case reported by Muscatello and cited by Boldrey and Elvidge.[5] Here the so-called epidermoid was an incidental finding, the principal lesion being an extradural dermoid with dermal sinus at a higher level. No pathologic details are given, and I have been unable to verify the original report. These tumors have been described as extramedullary in ten cases and as either intramedullary or subpial in nine cases. All of the latter have shown a definite connection with the pia. It is of interest that in two cases syringomyelic cavities have been found in the portions of the cord adjacent to the tumor, and in one case the entire central canal is described as abnormal.

Laminectomy was performed in fourteen of the cases of epidermoid tumor reviewed. Of these, eight were improved, although in two the tumor recurred. Six cases reported as improved had extramedullary tumors, and only two had intramedullary or subpial tumors. One case was reported as unimproved and two as worse; both of the latter were intramedullary tumors. There were two cases of postoperative death, and in one case the result was not mentioned. It appears, therefore, that the operative results, as in any other class of spinal cord tumor, depend largely on the position of the lesion in relation to the cord, being vastly better in the case of extramedullary lesions. As previously mentioned, the pathologic observations in the case reported here furnish an adequate reason for the poor results in dealing with intramedullary epidermoids, namely, the irregularity of the capsule with its many invaginations, including nervous tissue between its folds. For the same reason complete removal is rendered difficult, and recurrence is likely.

Dermoids.—The cases which I have selected include twenty-three dermoid tumors of the vertebral canal. In this group the onset of symptoms is considerably earlier than in the epidermoids. The first manifestation

appeared in the first decade in ten cases, in the second in five cases, in the third in four cases, and in the fourth in two cases. In two cases the age of onset is not given. Pain in the back and legs is the commonest early symptom, being mentioned in nine cases. This may be due to the fact that these tumors frequently occupy the lumbar portion of the canal where they tend to stretch the dura and nerve roots and may attain a considerable size before producing any neurologic deficit. In almost every case, however, symptoms of compression were present at the time of examination. Dermoids occur most commonly in the lower half of the canal, but one case of cervical tumor has been reported. In contrast to the epidermoids, they are oftener extramedullary than intramedullary, and in five cases the tumor has been entirely extradural. Only two cases of intramedullary dermoid have been reported. In three cases the tumor lay partly within and partly without the cord, spreading apart the posterior columns. In every case of extramedullary tumor the position has been dorsal to the cord. Spina bifida corresponding to the segmental position of the tumor has been reported in seven cases. Operation has been performed in nineteen cases with the following results: improved, nine; unimproved, two; recurred, 1; condition worse, 1; postoperative death, three; no mention, three.

A particularly interesting group of intraspinal dermoids are those associated with a congenital dermal sinus (pilonidal sinus). The pathogenesis and clinical features of these sinuses have been discussed by Walker and Bucy,[12] who reported the findings in seven cases which they had studied or had collected from the literature. A congenital dermal sinus, manifested externally by a small dimple in the midline of the back, discharges periodically serous or purulent material. The sinus extends to the meninges and its lumen acts as a pathway for infection to reach these structures. When this occurs, producing abscess formation, signs of meningeal irritation and weakness of the lower extremities develop. The spinal fluid, usually sterile, shows a pleocytosis. This malformation is usually associated with a spina bifida, but not necessarily so. The authors make no comment on the relationship of these sinuses to dermoid tumors within the spinal canal, and indeed in six of their cases there was no definite evidence of such a tumor. In one of their cases, however (Case 6, originally reported by W. and N. Sharpe), "A mass of caseous material containing hair was found imbedded between the dura and the left side of the spinal cord." No pathologic description of the tissue was given, but Walker and Bucy comment on the presence of hair at the base of the sinus as a "striking point." I am inclined to regard this finding as definite proof that they were dealing with an intradural dermoid cyst associated with an infected dermal sinus.

Among the reported cases of dermoid tumors of the vertebral canal I have found five similar cases, although in only two of these was there definite evidence of meningeal infection. In Ottonello's case, reviewed

in detail by Bradford,[4] a 20-year-old woman had had pain in the scapular region one year previously, followed by symptoms of progressive cord compression. A draining sinus at the third thoracic vertebra, which was obstructed in places, communicated through a bifid spinous process with a large, extramedullary, dermoid cyst. The symptoms in this case were apparently due to obstruction of the sinus with dilatation of the cyst rather than to infection of the cyst itself. Hipsley's case, also reviewed by Bradford,[4] is similar. In the second case reported by Boldrey and Elvidge,[5] a man, aged 45 years, showed symptoms of a cauda equina lesion following immediately upon excision of an anal fistula six years previously. At operation a cystic tumor lay among the roots of the cauda equina and was attached by a cystic cord to the tip of the conus. Microscopically the cyst was a typical dermoid, while the cord was composed of loose glial tissue containing portions of an ependyma-lined lumen. The authors assumed that the cyst represented the original point of attachment of filum terminale to skin, that it was pulled upward by normal growth processes, and that radical excision of the anal sinus released intravertebral attachments and abolished external drainage. Here again there was no evidence of infection. In the third case reported by Boldrey and Elvidge, a child 2½ years of age had a pigmented spot at the level of the lumbosacral joint, present since birth, which had discharged intermittently for nine months. For five months the child had had recurrent attacks of meningitis. The only neurologic finding, except for signs of meningitis, was absence of the ankle jerks. An infected dermoid cyst filled two-thirds of the lumbar canal and communicated with the sinus, which passed through a bifid spinous process. Finally, the case of Walker and Moore,[14] abstracted previously, should be included in this group. Here the onset of paraplegia followed immediately an attack of meningitis, and the intradural cyst was chronically infected.

That dermal sinuses communicating with the spinal canal are rare is evidenced by the observation of Rogers and Dwight,[20] who stated in 1938 that in a personal experience with some 400 cases of pilonidal sinus they had not yet seen one communicating with the neural canal. However, on the basis of the seven cases reported by Walker and Bucy and the five cases mentioned here, I feel that its occasional occurrence should be kept in mind in dealing with cases of recurrent unexplained meningitis or transverse myelitis, and that the presence of a cutaneous dimple in the midline of the back or a discharging sinus should constitute an indication for radical surgical exploration. The condition occurs most commonly in infants, four of the six patients being between 2 and 3 years of age at the time symptoms developed. Involvement of the cord or cauda equina may occur in two ways. The sinus may become obstructed, causing sebaceous secretion to accumulate within the cyst, which then enlarges and compresses the nervous structures; or

the cyst itself may become infected from the outside, giving rise to a localized meningitis or subdural abscess. In either case the symptoms are of sudden or rapid onset, and they tend to be intermittent.

SUMMARY

1. A case of subpial epidermoid tumor of the spinal cord in the lumbosacral region is reported. The peculiar histologic appearance of the tumor, in which the basement epithelial membrane is thrown up into innumerable folds, possibly accounts for the unsatisfactory surgical result which was obtained.

2. The literature of epidermoid and dermoid tumors of the vertebral canal is reviewed, using the collection of reported cases made by Boldrey and Elvidge, in 1939, as a basis. This collection is revised by eliminating doubtful cases and adding others, and it is believed that forty-two cases of this type of tumor have been reported. The addition of the present case brings the total to forty-three, of which twenty are probably epidermoids and twenty-three are probably dermoids.

3. In general, the epidermoids and dermoids behave very much as do other types of spinal tumor in similar locations. Certain aspects of their symptomatology deserve special mention. In the case of the epidermoids, sterile inflammatory reactions such as meningitis and acute transverse myelitis occasionally occur. There is some evidence that these are due to fatty acids formed within the cyst and liberated into the subarachnoid space. Dermoid tumors are occasionally associated with congenital dermal (pilonidal) sinuses. Obstruction of such a sinus may result in sudden exacerbation of pressure symptoms. Infection reaching the meninges via these sinuses may give rise to septic meningitis or localized subdural abscess.

4. The preoperative recognition of these tumors is not always possible, but a history of symptoms beginning early in life, the finding of a cutaneous dimple or a discharging sinus in the midline of the back, or the presence of spina bifida corresponding to the involved segment of the spinal cord, should suggest that one is dealing with a congenital cystic tumor of epidermoid or dermoid type.

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PARAPHYSIAL CYSTS OF THE THIRD VENTRICLE

Diagnosis and Surgical Management

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DESCRIBED under various names, reflecting uncertainty as to origin, the small, benign, encapsulated, cystic tumors occupying the third ventricle of the brain, for many years engaged the interest only of embryologists and pathologists. Clinical diagnosis eluded the neurologist. Could he have localized such a tumor by an inspired guess, few surgeons would have had the temerity to approach such a hidden and apparently inaccessible portion of the brain. The invention of cerebral pneumography and the modern refinements of neurosurgical technique made possible both the diagnosis and removal of these tumors.

In 1933, Dandy[1] included in his monograph on benign tumors of the third ventricle, experiences with the surgical treatment of five tumors which he termed colloid cysts, that name being purely a descriptive one. There were four successful results. In the same year, Zimmerman and German reported a case successfully operated upon by Harvey.[2] Since that time, there have been eleven additional successful operations.[3-9] All told, up until 1941, sixteen recoveries from twenty surgical attempts have been recorded. In addition, Zeitlin and Lichtenstein[10] refer to a recovery obtained by Oldberg. One of us (L. M. W.) has personal knowledge of two other recoveries, neither having been published. Judging from the published reports, one might get the impression that the rate of surgical recovery is high, but doubtless there have been surgical failures that have not found their way into the literature.

While the true relationship between surgical recovery and mortality rate is only speculative, it is probably less than is indicated by the previous figures. These tumors are rare, not more than 60 or 65 cases‡ having been recorded. In the majority of instances they have been unexpected post-mortem discoveries.

The embryology of paraphysial cysts, their clinical manifestations, and histologic variations have been thoroughly discussed in several extensive articles[3, 7, 9] so that little more than brief mention will be made of these features. In addition to reporting one more patient upon whom operation was performed successfully, it is our principal object to review the

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‡The various reviews cite different figures for the number of cases of paraphysial cysts reported. Stookey,[3] 1934, collected a total of 37 cases, McLean,[7] 1936, 49 cases, Rehbock,[19] 1936, 55 cases, Larson,[18] 1940, 57 cases and Zeitlin and Lichtenstein,[10] 1940, 68 cases.

diagnostic and operative methods used heretofore with tumors of this kind. Since only a few surgeons have had experience in removing these tumors, the pioneer methods developed in attacking the surgical problems have varied considerably. Paraphysial cysts are favorable lesions; therefore, it seems desirable at this time to pool all the experiences in order to establish a standardized surgical management.

CASE REPORT

R. D. F. (Case No. 99562).—The patient, a young married woman 22 years of age, was admitted to the Michael Reese Hospital Aug. 24, 1941. The patient had been entirely well until approximately three weeks before admission when she was awakened early one morning by an agonizing headache. She vomited in a few minutes. The headache gradually diminished but persisted throughout most of the day. The following morning the same sequence of events occurred; this repeated itself each succeeding day. By late afternoon, the headache generally wore off, and the patient was comfortable. The headaches were felt mainly in the frontal and occipital areas and were described as "pushing" or "pressing." Some weeks after operation the patient remembered that the headaches were associated with changes in posture, either setting in or becoming intensified when she was flat. She further recollected that when her husband urged her to lie down because she was ill, the headaches invariably became worse. They were less severe if she was "up and around." She found that when she propped herself up on pillows, the early morning headaches were less severe. Four or five days before admission she began to experience bouts of pain in the back of her neck which radiated down into her shoulders and arms. During these attacks, her hands felt numb and there was a "yoke of pain across the shoulders." A few days before admission she suddenly saw double and this difficulty persisted. There had been no previous illnesses or injuries. She had successfully completed a college course a year before, had married and was actively working on a farm at the time of the onset of her illness.

Physical Examination.—The general physical examination was entirely negative. She was a robust girl in apparent good health. No mental disturbances were observed. There was a palsy of both external recti muscles, the left more marked than the right. Examination of the fundi showed a bilateral papilledema of 4 diopters and the presence of many flame-shaped hemorrhages. Visual acuity was 20/30 in either eye and the visual fields were full. The remainder of the neurologic examination was essentially negative. Plain roentgenograms of her skull showed nothing remarkable. The clinical impression was brain tumor which, however, could not be localized. Ventriculography was deemed necessary to afford a precise diagnosis.

This was performed Aug. 29, 1941. Two burr holes were placed in the occipital region on either side. Both ventricles were struck at a depth of 3 cm. beneath the surface of the cortex. Two cubic centimeters of indigo-carmine dye were injected into the left lateral ventricle. The right lateral ventricle was then drained of fluid, 90 c.c. in all being obtained, but no dye appeared. It was evident from this observation that the intraventricular foramina on one or both sides were obstructed. The left lateral ventricle was then drained of fluid and an exchange with air made, 90 c.c. of fluid being obtained. The films showed a marked dilatation of both lateral ventricles (Fig. 1, *A*). No air was visualized within the third ventricle in any position of the head. The air shadows in both intraventricular foramina were sharply cut off (Fig. 1, *B*). A diagnosis was made of a tumor occupying the anterior portion of the third ventricle.

Twenty-four hours after ventriculography, the patient became drowsy, restless, and irrational. She complained of severe headache and loss of vision. She was able to distinguish only large moving objects. The second evening her pulse rate dropped

to 60 per minute and she became so torpid that it was necessary to tap the ventricles several times during the night. The fluid was under considerable pressure and after each tap she improved for a few hours. Operation was performed as an emergency measure Aug. 31, 1941.

Operation.—The operation was performed using only procaine infiltration of the scalp. A moderately large, right frontal osteoplastic flap was reflected, the dura opened in a circular fashion from the base upwards, and the dural flap reflected over the longitudinal sinus. A vertical (dorsoventral) transcortical incision, 5 cm. long, was made two inches anterior to the rolandic vein. The incision was carried down through the subcortex until the right lateral ventricle was entered. This was packed anteriorly and posteriorly with wet cotton to support the ventricular walls. Lighted retractors were introduced. The choroid plexus lying on the ventricular floor was identified and followed until it entered the foramen of Monro. The foramen was collapsed and appeared as a narrow slit below a thin, bulging septum lucidum. Because it appeared that it might be necessary to enlarge the foramen of Monro to gain access into the third ventricle, the terminal 1 cm. of the choroid plexus was coagulated with the electrosurgical unit. While the plexus was being handled with the bayonet forceps, traction was exerted slightly and for a moment a glistening tumor

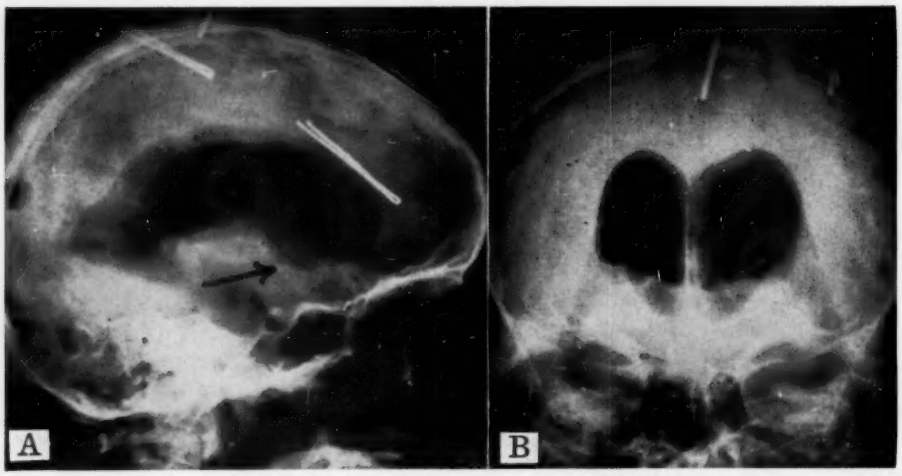

Fig. 1.—Both lateral ventricles are widely dilated, the left more than the right. The arrow in *A* points to the sharply cut-off air shadow in the dilated foramen of Monro. The third ventricle is not visible in any position of the head. Both lateral ventricles were punctured and the fluid exchanged for air. The septum lucidum is intact.

appeared in the orifice of the foramen of Monro. The tumor was grasped with another pair of forceps and with gentle teasing it was possible to slip the entire tumor through the foramen into the lateral ventricle. The tumor was about the size of a small cherry and appeared to be a thin-walled translucent cyst with fine vessels traversing the surface. It was attached to the portion of the choroid plexus within the third ventricle. This attachment was coagulated and cut. Slight bleeding followed from small veins about the foramen of Monro but these were controlled with cotton packs. Before withdrawing, the septum lucidum was punctured in order to insure drainage from the right to the left lateral ventricle, as it was anticipated that the right foramen of Monro might be blocked for a few days from edema. A thin split Penrose drain was placed within the lateral ventricle and brought out through a centrally placed incision in the dural flap which was tightly resutured in place. The bone flap was returned and wired into place and the drain led out be-

neath the skin flap through a posteriorly placed stab wound. The condition of the patient was good throughout the procedure and at the conclusion she was responding.

Postoperative Course.—Four hours after operation the patient was responding to questions and moving her left extremities weakly. For the first four days her general condition was good and she was quite bright, although the temperature rose as high as 103.6° F. There was copious drainage of slightly blood-tinged cerebrospinal fluid for the first forty-eight hours, after which period the drain was removed. On the fifth postoperative day the patient vomited a feeding and shortly thereafter had a left-sided Jacksonian convulsion lasting an hour. Her lateral ventricle was tapped and deeply bloody fluid obtained. It was suspected that the vomiting attack had "blown" a thrombus out of the end of a small intraventricular vessel. For the subsequent week she was torpid and restless, complained of severe pain in her neck, and was irrational from time to time. The temperature ranged between 100 and

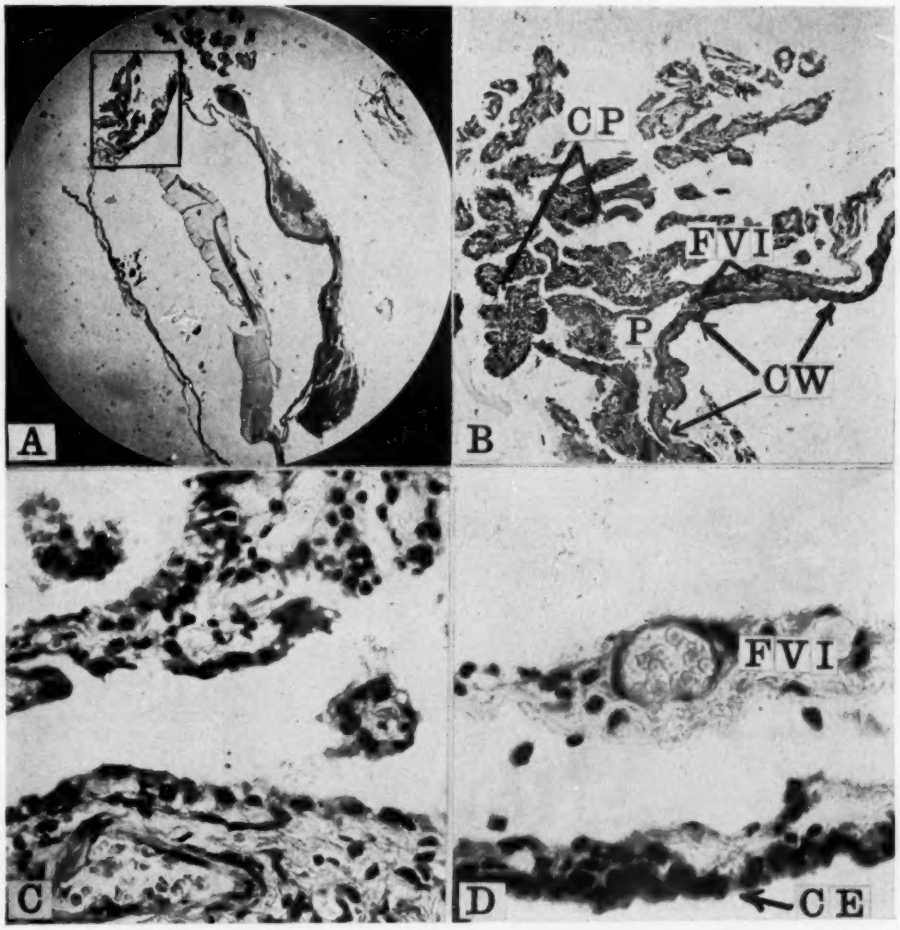

Fig. 2.—*A*, Cross section through the cyst enlarged about three times normal size. A small amount of homogeneously staining colloid material remains within the cyst.

B, An enlargement of the outlined square in *A*. The attachment of the choroid plexus *CP* to the cyst wall *CW* is clearly shown. The fusion of the two layers of the fibrovascular investment *FVI* derived from the tela choroidea is shown at the pedicle of the tumor *P*. It will be noted that the epithelial lining of the cyst has two layers of fused tela choroidea enclosing it, as indicated by the arrows beneath the letters *FVI*.

C and *D* are higher magnifications of the cyst wall. In *C* some areas of the epithelium are of columnar type. In *D* the typical single layer of ciliated cuboidal epithelium *CE* is shown.

102.6° F. but subsided gradually and became normal by the seventeenth postoperative day. At this time the ventricular and spinal fluid were xanthochromic. Indigo-carmine dye instilled in the right lateral ventricle was promptly recovered from the left ventricle and appeared also in the spinal canal in a few minutes. The power of her left extremities rapidly improved during the postoperative period, vision was returning and she became alert and cheerful. She was up in a wheel chair on the eighteenth day and walking on the twentieth. She was discharged twenty-one days after operation. At this time there was no gross weakness of the left extremities although a Babinski sign was present. The left angle of her mouth drooped slightly. The ocular palsies had disappeared and the papilledema was subsiding. She was able to read newsprint easily. Mental examination showed only a moderate psychomotor retardation and an unwarranted jocularity.

Fig. 3.—Photograph of the patient taken seven weeks after operation. The only residual neurologic sign at this time is a slight weakness of the left side of the face which is demonstrated by her smile.

Four months after operation, the patient had almost entirely recovered. She was taking full part in social activities and had returned to her farm work. Visual acuity was 20/20 in either eye and the visual fields appeared full. The fundi were normal with no evidence of optic atrophy. Neurologic examination was negative except for a slight weakness of the left angle of the mouth (Fig. 3). There were no complaints referable to the nervous system.

PATHOGENESIS AND ANATOMIC CONSIDERATIONS

Paraphysial cysts are now recognized as arising from the paraphysial body, an ancient gland situated in the midline of the rostral portion of the roof of the third ventricle.[11] It is found in all vertebrates and reaches an especially high development in amphibians and reptiles.[12] Francotte[13] first identified its presence in the early human embryo. Krabbe[14] found that its evolution and involution was rapid, the structure first appearing at about the seventy-fifth day of gestation (20 mm. stage) and disappearing shortly thereafter. In some individuals, remnants of the gland apparently persist throughout fetal life and presumably enlarge slowly during postnatal existence by retention of the products of the secreting epithelial cells. Indeed, small and clinically insignificant paraphysial cysts have been observed as incidental findings at autopsy.[14] McLean[7] has fully described the life histories of these tumors. As they increase in size and become heavier, they sag downward upon the tela choroidea and in this way are eventually enfolded by the layers of the tela (Fig. 4). This intimate investment by the tela choroidea has led to

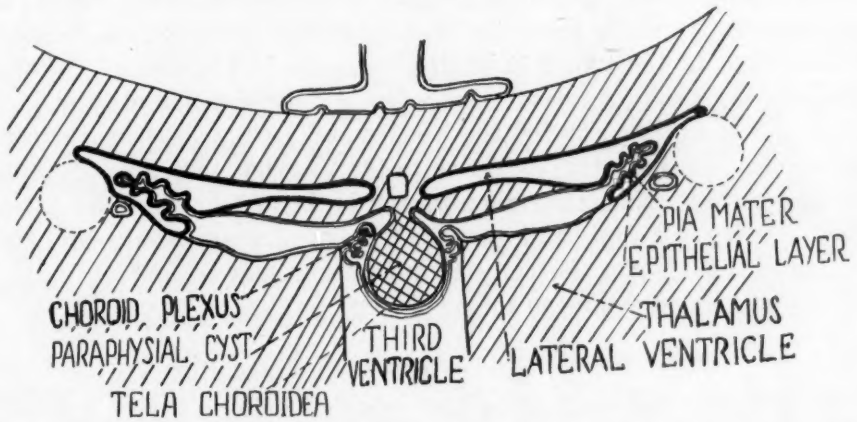

Fig. 4.—Adapted with modifications from Fig. 180 B of Larsell.[21] The formation of the primitive choroid plexuses is illustrated diagrammatically. A paraphysial cyst has been drawn in. It is shown sagging down upon the tela choroidea and, in turn, being enveloped by it. As the cyst enlarges and the pedicle thins, the choroid plexuses of the third ventricle will fuse at the pedicle. The cyst eventually is invested with the two layers of the tela choroidea which comprises the outer fibrovascular investment.

the erroneous conclusion by some writers that the cysts are derived from the choroid plexus. Although this pathogenetic conception is incorrect, these tumors are indeed intimately bound to the choroid plexus and tela choroidea. This raises surgical problems that will be more fully dealt with in later paragraphs. In time, if growth continues, the cyst enlarges until it occupies and fills the anterior portion of the third ventricle, eventually obstructing the intraventricular foramina. Since the tumors are exactly in the midline and are usually round, both foramina are likely to be blocked equally. The interference with drainage of the cerebrospinal fluid from the lateral ventricles into the third ventricle

ultimately results in a dilatation of the lateral ventricles which is generally symmetrical. Since, in some cases, the duration of symptoms has been short while necropsy or ventriculographic study has disclosed very large lateral ventricles, the conclusion seems inescapable that gradual dilatation of these chambers from an incomplete block may occur and yet cause no symptoms. The onset of violent headache, vomiting, and papilledema apparently occurs when the last bit of flow through the intraventricular foramina of one or both ventricles is completely obstructed. There is considerable reason to believe that impaction of the tumor into one or both foramina may occur for transient periods. Such episodes are marked by the sudden appearance of pronounced evidences of intracranial hypertension. The symptoms may subside even as abruptly. The explanation for this curious phenomenon is the fact that there is a certain degree of mobility to these pendulous tumors which hang from the roof of the third ventricle. A change in position of the head may dislodge the tumor enough to obstruct the intraventricular foramina suddenly and completely. Stookey thinks that yet another mechanism comes into play. The lesser veins of Galen are formed within the intraventricular foramina by the confluence of the veins of the choroid plexus and the veins draining the caudate nucleus and thalamus. Dislodgment of the tumor through alterations in position of the head, according to Stookey,[3] compresses the lesser veins of Galen at their origin causing venostatic edema of the basal ganglia as well as an increased secretion of cerebrospinal fluid due to the raised venous pressure in the choroid plexus. This latter phenomenon is thought to produce a vicious circle leading to a rapid and great increase of pressure within the lateral ventricles. Whatever the correct explanation may be, sudden death is not an uncommon ending to these episodes.

DIAGNOSIS

As McLean pointed out, the third ventricle being a cavity, tumors in it can have no distinctive symptomatology except those due to an obstructive hydrocephalus. Yet adventitious neurologic symptoms and signs may, and frequently do, appear from direct compression of neighboring neural structures. Direct injury of the hypothalamic nuclei in the floor and walls of the third ventricle may give rise to diabetes insipidus, obesity and genital dystrophy, and on several occasions has produced curious attacks characterized by flushing, lacrimation, sweating, and other evidences of a diffuse sympathetic discharge, the so-called diencephalic epilepsy of Penfield.[16] Focal paralyses and oculomotor disturbances have also been noted and many other neural disturbances for which the pathogenetic explanation is not clear. However, analysis of the numerous published protocols easily convinces one that no syndrome can be constructed which is typically produced by these tumors. While most neurologic writers subscribe to this view, some believe that a diagnostic symptom is the occurrence of violent headache with alteration in

the position of the head. An explanation of this has been given in a previous paragraph. It must be pointed out, however, that the spectacular character of the phenomenon has made a greater impression than is warranted by the number of cases in which it has been seen. In those cases in which the patient came to operation, the sign was observed only in five instances (Table I) and in our case, which is included in the five, its existence became known only long after operation when the patient was pointedly questioned. Stookey found in an analysis of the literature that 39 per cent of patients had this symptom.[3] Nevertheless, it must be admitted that this sign, while suggestive, is not pathognomonic since it is occasionally observed with tumors of the fourth ventricle or those within the lateral ventricle. There have been three instances where the correct diagnosis was suspected or at least suggested and in none of these were postural headaches observed. More common but less dramatic has been the intermittency of the symptoms, periods of violent headache and vomiting appearing and vanishing with comfortable or entirely symptom-free intervals. This fact is perhaps of statistical value, but again surgeons of experience would hardly venture a diagnosis of tumor within the third ventricle on this ground alone, since intermittent headaches are so commonly experienced from tumors of various kinds in different locations.

Not only is a syndrome diagnostic of these tumors lacking, but a review of the literature reveals the somewhat astonishing fact that they may exist without producing evidence of intracranial hypertension although they cause other ominous symptoms. Slowly progressive dementia,[17, 18] a chronic convulsive state, primary optic atrophy, and other symptoms not ordinarily ascribed to intracranial pressure may comprise the clinical picture of paraphysial cysts.

Again, the histories of cases with paraphysial cysts show so many vagaries that little is obtained for diagnostic purposes from a study of the records. The first manifestations may announce themselves with apoplectiform rapidity, sudden coma and death terminating in a few hours what has apparently been a healthful life.[18] On the other hand, neurologic evidence for what appears to be diffuse degeneration of the nervous system may exist for years, symptoms of tumor being conspicuous by their absence. These considerations lead one to the view that diagnosis, with rare exceptions, depends upon evidence afforded by pneumography. Indeed, in operations which have been carried out for paraphysial cysts, pneumographic study has been relied upon as the final arbiter and in every instance has preceded surgery, the pre-pneumographic diagnosis usually having been unlocalized brain tumor.

The details of the pneumographic findings have been carefully described, first by Dandy[1] and later more fully by Davidoff and Dyke.[5] They vary somewhat, minor differences depending upon the completeness of the block of the intraventricular foramina, the integrity of the septum

TABLE

SUMMARY OF CLINICAL, DIAGNOSTIC, AND OPERATIVE

AUTHORS AND SURGEONS	AGE AND SEX	DURATION OF SYMPTOMS	CLINICAL HISTORY	NEUROLOGIC FINDINGS
W. E. Dandy Case 1 1933	24 F	9 Mo.	Severe and continuous headaches	Bilateral papilledema of 6 diopters; weakness of right sixth nerve
W. E. Dandy Case 2 1933	34 F	10 Yr.	Recurrent bouts of headache and vomiting; fainting spells; disturbances in equilibrium, diplopia, and failing memory	Mentally dull; bilateral papilledema; slight bilateral exophthalmos; suggestive Romberg sign
W. E. Dandy Case 3 1933	10 F	8 Mo.	Repeated bouts of headache; one tonic convulsion; diplopia and strabismus	Enlarged head; bilateral papilledema, strabismus; diagnosis of intraventricular tumor made on basis of periodic attacks
W. E. Dandy Case 5 1933	37 F	5 Yr.	Repeated bouts of severe headache, dizziness and vomiting precipitated by change in position of head; occasional loss of consciousness in attacks and bradycardia as low as 44 per minute in attacks	Neurologic examination negative, fundi normal, ventriculography performed because of history
H. M. Zimmerman, and W. J. German Case 1, 1933 (Operation by Sam Harvey)	26 M	4 Yr.	Recurrent attacks of headache, weakness and drowsiness of increasing severity and frequency; two episodes of unconsciousness; sweating and flushing attacks; blurring of vision	Bilateral papilledema of 4 diopters; clinical impression, tumor of third ventricle
Byron Stookey Case 2 1934	43 M	7 Mo.	Severe bitemporal headache, blurring of vision, tinnitus	Bilateral papilledema of 2 to 3 diopters
Byron Stookey Case 3 1934	31 M	1 Yr.	Onset with spells of dizziness and weakness; later continuous headaches and drowsiness, polydipsia and polyuria, exophthalmos; one fainting spell	Bilateral papilledema and bilateral exophthalmos; obesity and hirsutism
C. B. Mason Case 2 1934	23 F	5 Yr. (?)	One week severe headaches followed by 5-year symptom-free interval; one month before admission developed severe headaches and series of convulsions, vomiting attacks and failing vision	Bilateral papilledema, reduced vision, inferior nasal defect in field of right eye; clinical impression, tumor of third ventricle or bifrontal tumor

I

DATA ON 17 CASES OF PARAPHYSIAL CYSTS

PNEUMOGRAPHIC DIAGNOSIS AND FINDINGS	METHOD OF OPERATIVE REMOVAL	POSTOPERATIVE COURSE AND RESULTS
Ventriculography; both lateral ventricles dilated and not communicating, no third ventricle visible	Right hemisphere retracted from falx; corpus callosum split and body of right lateral ventricle entered. Foramen of Monro identified and margin split anteriorly, tumor removed in toto	Stormy; temp. 102 to 104° F. for 17 days; light hemiplegia. Hemiparesis 10½ years later
Ventriculography; marked dilatation of both lateral ventricles which intercommunicated through ruptured septum; no third ventricle visible	Left hemisphere retracted from falx; posterior half of corpus callosum split and tela choroidea divided. Cyst aspirated and wall dissected free	Temp. 99 to 102° F. for 17 days; complete recovery
Ventriculography; air injected in one lateral ventricle showed dilatation but did not pass to other lateral ventricle. Some air seen in the third ventricle which outlined filling defect in the anterior portion	Horseshoe-shaped block of tissue resected from right frontal lobe and lateral ventricle entered; anterior margin of foramen of Monro split, cyst aspirated, and wall dissected free	Uneventful recovery
Ventriculography; huge dilatation of both lateral ventricles. No air visible in the third ventricle	Right occipital craniotomy and posterior portion of right hemisphere retracted from falx. Corpus callosum split and lateral ventricle entered; foramen identified and enlarged anteriorly, cyst contents aspirated, and wall dissected free.	Mental confusion and spatial disorientation for several weeks; abnormal temperature for 5 weeks. Well 6 months later except for mild mental disturbances
Ventriculography; both ventricles injected and huge dilatation observed. No third ventricle visible	Two-stage operation; first stage transcortical incision through right frontal lobe into lateral ventricle and tumor visualized. Second stage, ventricle re-entered, foramen of Monro enlarged posteriorly, tumor dissected free from choroid plexus	Fever 101° F. for one week, then uneventful recovery
Encephalography; lateral ventricles dilated. Air in the third ventricle outlining tumor in the anterior portion	First stage, right subtemporal decompression. Second stage, transcortical incision through right frontal lobe into lateral ventricle. Cyst extracted through dilated foramen of Monro	Visual impairment and disorientation for 4 weeks; complete recovery in 3 months
Ventriculography; both lateral ventricles greatly dilated. No third ventricle visualized	Transcortical incision through right frontal lobe into lateral ventricle; tumor seen filling dilated foramen of Monro, cyst contents aspirated, and wall dissected free	Uneventful and complete recovery except for poor vision
Ventriculography; dilated lateral ventricles communicating. Air in the third ventricle outlining a tumor in the anterior portion	Transcortical incision in right frontal lobe made through small horizontal dural slit. Lateral ventricle entered, foramen of Monro enlarged anteriorly, cyst contents curetted out, and wall dissected free	Uneventful and complete recovery

AUTHORS AND SURGEONS	AGE AND SEX	DURATION OF SYMPTOMS	CLINICAL HISTORY	NEUROLOGIC FINDINGS
L. M. Davidoff, and C. Dyke Case 4 1935	19 M	10 Mo.	Severe headaches induced by flexion of neck; headaches progressively more severe, flashes before eyes, one fainting spell	Bilateral papilledema
L. M. Davidoff, and C. Dyke Case 5 1935	27 F	6 Yr.	Early complaints of mild intermittent headaches, transient blurring of vision and one convulsion; later severe headaches induced by change of posture	Bilateral papilledema
L. M. Davidoff, and C. Dyke Case 7 1935	27 F	2 Mo.	Sudden onset of severe continuous temporal and frontal headaches	Bilateral papilledema
J. F. Paterson, and M. Leslie 1935	34 M	2½ Yr.	Recurrent attacks of headaches becoming more severe and accompanied by dizziness, vomiting and unconsciousness; progressive visual failure	Bilateral papilledema; vision half reduced
A. J. McLean Case 2 1936	16 F	4 Mo.	Amblyopia on change of posture; recurrent attacks of headache and vomiting induced and relieved by change in posture; diplopia	Bilateral papilledema, weakness of right external rectus, left central facial weakness, nystagmus, unsteadiness of gait, dysmetria and ataxia of arms; clinical impression, chronic arachnoiditis
W. J. Gardner, and O. Turner 1937	31 F	10 Mo.	Severe frontal headaches and attacks of head pain; failing vision	Bilateral papilledema; intraspinal pressure, 250-300 mm. of water
M. A. Shaver Case 1, 1940 (Surgeon W. S. Keith)	26 F	2 Yr.	Recurrent attacks of headache and vomiting becoming progressively more severe	Bilateral papilledema
M. A. Shaver Case 2, 1940 (Surgeon, K. G. McKensie)	28 F	5 Mo.	Progressive visual failure	Bilateral papilledema
L. M. Weinberger, and B. Boshes 1942	22 F	3 Wk.	Sudden onset of severe continuous headaches associated with vomiting attacks; headaches aggravated by supine position, relieved by erect posture; diplopia	Bilateral papilledema of 6 diopters; bilateral external rectus palsies; clinical impression, unlocalizable brain tumor

TABLE I—CONT'D

PNEUMOGRAPHIC DIAGNOSIS AND FINDINGS	METHOD OF OPERATIVE REMOVAL	POSTOPERATIVE COURSE AND RESULTS
Encephalography; symmetrical dilatation of lateral ventricles. Air in the third ventricle outlining a tumor in the anterior portion	Transcortical incision through right frontal lobe into lateral ventricle. Tumor seen in dilated foramen of Monro. Cyst aspirated and wall dissected free	Moderate fever 3 weeks and then complete recovery
Ventriculography; both lateral ventricles dilated. No third ventricle visible and air shadows in foramina of Monro sharply cut off. Shadow of tumor seen between lateral ventricles	Transcortical incision through right frontal lobe into lateral ventricle. Tumor seen in dilated foramen of Monro. Cyst contents evacuated and wall dissected free	Fever for several weeks; recovery. Status(?)
Encephalography; lateral ventricles dilated. Air in third ventricle outlined tumor in anterior portion	Transcortical incision through right frontal lobe into lateral ventricle. Cystic tumor projected through dilated foramen of Monro, cyst contents removed, and wall dissected free	Stuporous and hemiplegic for several days; moderate hemiparesis and mental confusion 6 weeks later
Ventriculography; marked dilatation of both lateral ventricles. No third ventricle visible. Indigo-carmine dye passed readily from one lateral ventricle to other through ruptured septum lucidum	Block of right frontal lobe resected and ventricle entered. Tumor seen in dilated foramen which was enlarged anteriorly; tumor removed in toto	Fever for 6 days up to 102.4° F.; mental confusion for 2 weeks. Two convulsions in postoperative period and complete recovery in 8 months
Ventriculography; one lateral ventricle was injected and appeared markedly dilated. Air did not cross to other lateral ventricle but a small amount was seen in the third ventricle which outlined filling defect in anterior portion	Wedge-shaped block of tissue resected from left frontal lobe and lateral ventricle entered. Tumor blocked foramen of Monro. Cyst evacuated and wall dissected free; moderate hemorrhage	High fever for 5 weeks; bloody C.F.S.; coarse tremors, complete recovery in 8 months except for slight aphasia
Ventriculo-encephalography; dilated lateral ventricles. Posterior portion of the third ventricle visualized with air outlining tumor in anterior portion. Indigo-carmine dye passed from one lateral ventricle to other	Transcortical incision through right frontal lobe into lateral ventricle. Tumor presented in foramen of Monro which was enlarged anteriorly. Cyst evacuated and capsule dissected free	Uneventful and complete recovery
Ventriculography; large dilated lateral ventricles. No third ventricle visualized	Transcortical incision through right frontal lobe into lateral ventricle. Tumor presented in foramen of Monro which was enlarged anteriorly, cyst evacuated and capsule dissected free	Uneventful and complete recovery except for epilepsy controlled by barbiturates
Ventriculography; one lateral ventricle injected with air and appeared dilated. No air visualized in other lateral ventricle or in third ventricle	Transcortical incision through right frontal lobe into lateral ventricle; cyst presented in foramen of Monro which was enlarged anterosuperiorly. Cyst removed in toto	Slight fever, complete recovery
Ventriculography; air injected into both lateral ventricles, both ventricles dilated; third ventricle not visualized. Indigo-carmine dye injected into one lateral ventricle did not pass to other	Transcortical incision through right frontal lobe into lateral ventricle. Cyst grasped by instrument inserted into third ventricle and withdrawn through foramen of Monro	Moderate fever for 2 weeks, intraventricular hemorrhage, weakness of left extremities; complete recovery in 3 months

lucidum, the type of air study (ventriculography or encephalography), and whether one or both ventricles are punctured in the performance of ventriculography.

Although Davidoff and Dyke[5] and Stookey[3] performed encephalography in three cases and succeeded in diagnosing the tumors, it is the opinion of most neurosurgeons that the presence of intracranial hypertension makes this procedure hazardous, especially so in the light of recent knowledge respecting the mechanism of tentorial herniation. Their encephalographic findings, however, are summarized in Table I.

If bilateral burr holes are made and both lateral ventricles cannulated, a characteristic ventriculogram is obtained. Both lateral ventricles appear dilated, and occasionally enormously so; they are usually symmetrical. No air is visualized within the third ventricle in any position of the head. The foramina of Monro are dilated but the air shadows are sharply cut off (Fig. 1). Occasionally, in the anteroposterior projections, the convex outlines of the tumor may be seen bulging into one or both lateral ventricles. Rarely, the block of the intraventricular foramina may not be complete so that a little air enters the third ventricle and outlines the tumor.

If only one lateral ventricle is cannulated and the septum lucidum is intact, no air will escape from the ventricle and the roentgen film will show a single dilated lateral ventricle. On the other hand, if the septum lucidum is frayed and torn, as is frequently the case, air will pass through it and both ventricles will be visualized. With either of these two circumstances, interpretation may be confusing since the question of a technical fault may arise. The suspicion may occur that the absence of air in the third ventricle is due to inadequate drainage of the ventricular system or to inadequate diffusion of air throughout the system. For these reasons it seems that less difficulty in roentgen interpretation will be encountered if both ventricles are injected with air at the same time.

Preliminary to air injection, it is common practice to instill a few cubic centimeters of indigo-carmine dye into one lateral ventricle and then attempt to recover it from the other; failure to do so indicates a block of the intraventricular foramina, while passage of the dye is generally taken to indicate free communication. It may be misleading to rely upon the passage of dye, as several observers have pointed out[6] that dye may pass through, owing to rupture of the septum lucidum or to an incomplete block of the foramina of Monro although a large tumor may be present.

OPERATIVE TECHNIQUE

Operation should be undertaken when the ventriculographic diagnosis is made. It seems that disaster is particularly prone to occur after ventriculography, with third ventricle tumors, if the patients are not operated upon promptly. In our own case a fatality was avoided only

by repeated ventricular punctures during the forty-eight hours that intervened between diagnosis and operation.

Due to the infrequency of paraphysial cysts, methods of operation have varied considerably in regard both to the anatomic approach and the details of surgical technique. Dandy, in his early experiences, used three different methods of attacking these tumors. In his first case he retracted the right hemisphere from the falx in the parietal region, split the corpus callosum and entered into the right lateral ventricle. Working within the lateral ventricle, he removed the tumor through the foramen of Monro. In his second case, he retracted the right hemisphere from the falx, split the corpus callosum and tela choroidea, and entered directly into the third ventricle thus exposing and subsequently removing the tumor. In his third case, he resected a large block of tissue from the right frontal lobe and entered the lateral ventricle opposite to the foramen of Monro and removed the tumor through the foramen. It is our impression, gained from his subsequent writings,[20] that he favors the last method. All other operators who have succeeded in removing paraphysial cysts have adopted the transcortical method of entering the lateral ventricle. This seems to carry less hazards than the transcollosal route for several reasons. It avoids retraction of the hemisphere and ligature of the veins entering the longitudinal sinus, maneuvers which are likely to cause swelling of the hemisphere. It avoids dealing with the veins of Galen. Lastly, by offering a direct route to the foramen of Monro, the exposure is more ample, hemorrhage can be more easily dealt with, and there is less possibility of injuring vital neural structures.

Dandy,[1] Paterson and Leslie,[6] and McLean[7] have resected round or wedge-shaped blocks of tissue from the frontal lobe in order to gain access to the lateral ventricle but this seems to be an unnecessary sacrifice of brain substance and offers slight or no advantage over a simple linear transcortical incision. The incision should be made well anterior to the motor cortex and preferably at right angles to it. The advantage of a horizontally placed incision is that the pressure and contusing effects of retraction are not exerted against the motor cortex as they are if the incision is made in a vertical (dorsoventral) direction. This precaution makes it easier to avoid a postoperative hemiplegia. In our own case, there was a moderate weakness of the left extremities for several days and in some cases the weakness has been marked and persistent.

Since paraphysial cysts lie exactly in the midline, there is no occasion ever to approach the tumor from the left side. Where this has been done by McLean and by Dandy, aphasic disturbances or defects in spatial orientation have followed.

It is our impression that operation for a paraphysial cyst should be performed in one stage. While Harvey[2] and Stookey[3] succeeded in accomplishing two-stage removals, there have been two other cases where death has occurred between the first and second stage.[2, 3] Operative trauma with its attendant cerebral swelling and disturbance of the intracranial

hydrodynamics seems to carry a much greater hazard if the tumor is not removed and the ventricular block released. For this reason, unless the desperate condition of the patient does not permit, all efforts should be made to remove the tumor at one sitting. This also applies to those rare instances in which the lateral ventricles are not sufficiently dilated for surgical maneuvers to be carried out easily within the ventricle. A preliminary subtemporal decompression to allow enlargement of the ventricle with the period of necessary waiting may be more dangerous than attempting to work within a small ventricle.

The experience of surgeons who have successfully removed paraphysial cysts shows that ample working room is obtained within the dilated lateral ventricle. The structures are seen clearly with the aid of illuminated retractors which may be easily introduced within the ventricle. The foramen of Monro may be found promptly by following the choroid plexus forward until it is seen to disappear. The cyst, if large, presents itself as a greenish or bluish mass in a dilated foramen, and this is the usual finding. If small, it may not be visible and the foramen may appear as a small slit. By tugging gently on the choroid plexus, the cyst wall can be brought into view in the aperture of the foramen and then grasped with an instrument. In our case, it was possible thus to tease the cyst through the foramen, but if the tumor is quite large, one must resort to other methods of delivery.

Some operators have first evacuated the thick colloidal contents of the cyst by aspiration and then delivered the capsule through the foramen. Others have enlarged the foramen by slitting its margin. The slit can be made safely only in the anterior rim of the foramen which is formed by the descending pillars of the fornix. Several small veins lie in this region, the largest of which is the vein of the septum lucidum. These may be coagulated easily and the enlarging of the foramen becomes a bloodless procedure.

As pointed out earlier, the paraphysial cyst is intimately connected to the choroid plexus and the tela choroidea, but this is its only point of attachment. When the cyst or the cyst wall is in full view this attachment can be readily clipped or coagulated and the cyst cut free. This is a simple but important step, for should the cyst be inadvertently torn away, severe hemorrhage, difficult to control, will result and the floor of the third ventricle be injured in the attempt to handle the bleeding.

Since the manipulations around the foramen may produce edema and thus obstruct drainage of the ventricle for a few days, it is worth while taking the precaution of tearing a small opening in the septum lucidum, if one is not already present. The occurrence of cerebral swelling as a consequence of operative manipulations may require drainage of the ventricle for a few days with a Penrose drain or an indwelling cannula. Drainage also serves to remove blood and detritus from the ventricle which, if not removed, may not only cause fever but conceivably may ob-

struct the cerebral aqueduct. The patient in Dandy's[1] fifth case died after a stormy postoperative course from obstruction of the aqueduct.

If the patients survive the operative procedure and the immediate postoperative course, complete recovery is generally to be expected. From this point of view, paraphysial cysts are extremely favorable tumors. Of the 17 cases operated upon, 13 showed complete or almost complete recovery, 2 had residual hemiparesis, 1 had a mild residual aphasia, and 1 was neurologically normal but had epilepsy which was controlled with barbiturates. One of the cases of hemiparesis was reported only six weeks after operation[5] and further recovery very likely took place.

If the incision through the cortex is placed well anterior to the motor strip, complete recovery should follow operation, since removal of the tumor ordinarily entails no trauma to vital structures and normal ventricular drainage is promptly established. Focal epilepsy should be an uncommon sequel as little glial scar forms when the incision is carried down to the ventricle.

In only one case has a postoperative pneumogram been performed, but in this instance the ventricular system was entirely patent.

SUMMARY

An additional case is recorded of a successful removal of a paraphysial cyst, thus bringing the number of reported surgical recoveries to seventeen. In an effort to standardize the surgical management of these tumors, the literature is reviewed and certain conclusions reached concerning the most favorable methods and the techniques to be employed in both diagnosis and operation.

Addendum

Fourteen months after operation, the patient writes that she is entirely well and is working full time. There have been two brief attacks consisting of twitching of the left side of the face but with no loss of consciousness.

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THE USE OF DETERGENTS IN THE CLEANSING AND LOCAL TREATMENT OF BURNS

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IN CIVIL life, the most common causes of burns are (1) fire, (2) hot liquids, (3) contacts with hot surfaces, (4) electric burns, (5) chemical burns, and (6) sunburn.[1] The common contaminants of such injuries are the various forms of particulate soil and the charred remnants of clothing. Fuel oil and grease are sometimes found on burned surfaces following automobile and the occasional maritime accidents. The usual reason for the presence of oil-, fat-, or grease-covered burns in civilian practice is the application of these substances to the burned area either by the patient or someone rendering first aid.[1]

In time of war, however, different types of burns result. They are more frequent and severe and occur under conditions which may render emergency treatment difficult. War burns are most often due to (1) gun or bomb flash, (2) boiling or burning oil, especially in disasters at sea, (3) incendiary bombs, (4) gasoline explosions, (5) electricity, and (6) chemicals (mustard gas, phosphorus, etc.).[2] Besides the delay which is often incurred before proper treatment can be instituted, these burns are usually contaminated by particulate soil, charred clothing, and often by heavy coats of grease and hydrocarbon oils. There may be other injuries in addition.

The difficulties encountered in cleansing and débridement are obvious, and the inadequacies of most cleansing methods used at present have been admitted by workers in the field. This is especially true in burns contaminated by greases and oils. Indeed in certain such cases subsequent tanning procedures have proved to be inefficient or have had to be omitted.[3] The literature, both before and during the present world conflict, abounds in references emphasizing the lack of a cleansing method which would not subject the already shocked patient to general anesthesia and in which vigorous scrubbing with soaps and irritating solvents would not be necessary. These latter methods often injure or remove healthy tissue.[4, 5]

The coagulation treatment of burns appears to be efficient and in many cases practical.[6] The eschar, when formed on a relatively clean surface by tannic acid, gentian violet, triple dye, or the like, accomplishes many purposes: (1) it prevents the loss of fluid, electrolytes, and protein from the burned surface; (2) it is an efficient barrier against exogenous infection, especially dangerous in the critical, early period

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TABLE I

ANALYSIS OF PRELIMINARY CLEANSING METHODS EMPLOYED IN THE TREATMENT OF BURNS

CLEANSING METHOD	SEDATION	TREATMENT TO FOLLOW	REMARKS
Slight superficial cleansing	Morphine	Saline baths and dressings	Bulky; much nursing needed; only a few patients can be treated; danger of infection
Slight superficial cleansing	Morphine	Triethanolamine*-sulfadiazine spray[21]	Potentially infected material left behind; sulfadiazine not all-powerful
Moderate, gentle scrubbing and débridement (white soap and water)	Morphine	Vaseline gauze and pressure dressings[22] Tanning or coagulation[23, 24]	No effective removal of layers of grease or oil
Moderate to considerable scrubbing with saline or green soap and water Ether soaps, grease solvents Moderate to considerable débridement	Morphine, general anesthesia	Tanning or coagulation[5, 26]	Shock increased by scrubbing and anesthesia; healthy tissue injured or removed by solvents and scrubbing methods

*Triethanolamine has detergent properties but is employed in the above mixture for its penetrant and solvent qualities.

of treatment; (3) it further decreases the incidence of shock by rapidly diminishing pain; and (4) it allows for greater ease in nursing and in transportation. Other methods offer no such advantages. Saline baths are efficacious when adequate nursing and hospital facilities are available but are not practical in widespread disasters.[4]

Infection is the great complication in the coagulation treatment and, indeed, in any proscribed treatment for burns. The probable origin of most suppuration occurring under "tans" is the initial contamination which had never been fully eradicated.[4] Certain infections may have their portal of entry at the edges of the eschar or in cracks in its surface.

More recently, in preference to coagulation procedures, immobilization by pressure dressings has been suggested as a more effective treatment than tanning.[22]

In the past few years, a group of chemical compounds, the so-called synthetic detergents, have gained wide use, at first in industry and more recently in dermatology. Detergents are substances in which the cleansing properties are dependent on a bipolarity of chemical structure. Most of these substances show a hydrophilic, or water-attracting, group and a hydrophobic group which finds its greatest attraction toward solids and liquids not easily wet by water (that is, certain particulate soil, oils, and greases).

Many types of agents present these necessary chemical groups in their molecular structure. They are listed in Table II.

TABLE II

A LIST OF THE MAIN TYPES OF DETERGENT MOLECULES*

1. Sulfonated vegetable or animal oils
2. Sulfated alcohols
3. Sulfonated fatty esters or amides
4. Sulfonated alkylated aromatic hydrocarbons
5. Sulfonated ethers
6. Sulfonated aliphatic di-esters
7. Phosphated or borated fatty alcohols
8. Sulfonated hydrocarbons
9. Fatty amine salts

*After Lane and Blank.[7]

The mechanism of action becomes apparent when a substance with such remarkable bipolarity is mechanically distributed throughout a water-insoluble medium, either particulate or homogeneous. The hydrophobic pole will orient and fix itself about the particle or molecule of

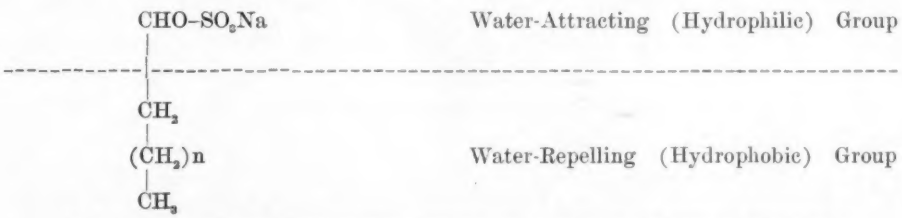

Fig. 1.—The diagrammatic configuration of a simple synthetic detergent.

homogeneous substance (oil), leaving its hydrophilic, or water-attracting, pole projecting outward in radial fashion (Fig. 2). A particle or molecule thus coated has an external layer of a water-soluble or a water-attracting group which renders the particle "solubilized," or more easily influenced by water.

Because the hydrophobic pole of the detergent is attracted to water-repelling substances, these agents are endowed with a variable amount of penetrating power, due to the attempt of this attraction to satisfy itself. The amount of mechanical agitation necessary to distribute uniformly a detergent through a layer of grease so that the entire grease layer may be subsequently washed off with water depends on the penetrating power of the particular detergent or detergent mixture employed.

Synthetic detergents are particularly fitted for the cleansing and débridement of those burns contaminated with and covered by a layer of grease, oil, and particulate matter. Most of them are nonirritating and have a pH which varies from neutrality to moderate alkalinity. Many have been used repeatedly and for long periods as soap substitutes for sensitive skins and as ingredients in dermatologic ointments.[7, 8, 9, 10] Nearly all of them have bacteriostatic and some bactericidal power, especially for the cocci found on the skin,[11, 13, 14, 15, 16] and many have proved

noninjurious to animals, even after prolonged oral and parenteral administration.[17] As an antiseptic, the application of some of the synthetic detergents to wounds and even to empyema cavities has already been tried either alone or with other antibacterial agents.[11, 12, 14, 25] One could hardly desire a more compatible array of qualities.

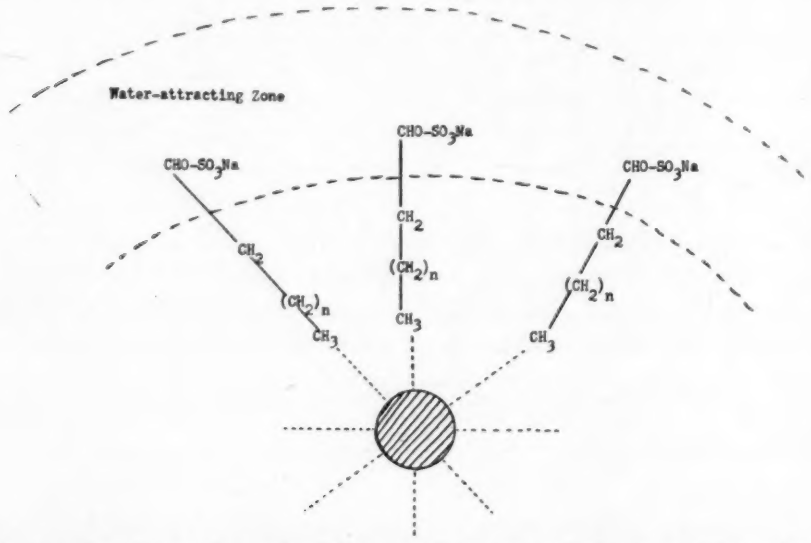

Fig. 2.—The hydrophobic poles of the detergent molecules coat and are adsorbed at the surface of the nonwetting, water-repelling particle or molecule. The hydrophilic poles project away from the particle to form a halo of water-attracting groups, thus "solubilizing" the particle of soil or molecule of grease.

Nearly 100 tests, each employing a different single detergent or detergent mixture, have been made on the normal, intact human skin. These experiments were all of a similar nature. Their purpose was to determine the effectiveness of the agent or mixture tested in removing from a given surface a layer of grease, oil, or fat, often purposely contaminated with particulate matter. The time and mechanical force necessary to disperse the agent throughout the grease or oil was also estimated and considered in the evaluation. Some six different mixtures proved most effective and required the least mechanical dispersion before the layer of grease was thoroughly and uniformly mixed with the agents used. With all of the effective mixtures, running water would then, within a few seconds, wash off the grease-detergent or oil-detergent combination. A clean skin remained, which, when dried by blotting, presented a definitely nongreasy feel, drier even than untreated normal skin. In other words, not only had the applied grease or oil been effectively removed, but along with it the natural skin oils, leaving a surface ready for the application of dye or water-soluble tanning agent. No signs or symptoms of skin irritation resulted except dryness, which occurred after repeated use. All of the mixtures listed in Table III in comparative tests proved to be cleansing agents far superior to green soap and water.

Since the cleansing of a given burned area is carried out only once, more powerful detergent combinations and stronger concentrations may be employed than would be considered suitable for repeated use (such as a soap substitute). Also, as a careful study of Table III reveals, it has been possible to employ adjuvant penetrant agents in some mixtures to lessen the amount of mechanical dispersing force necessary to distribute the detergent throughout the grease layer. No irritation resulted from the application of these penetrating agents to small skin areas or to relatively small burned areas in clinical cases.

The composition of certain detergent mixtures was based upon the following theoretical concept which subsequently proved to be efficacious in actual practice. For a long time it has been known that oils are detergents in a sense, and it has been found that grease and heavy oils may be removed from the skin by rubbing a readily mixing fat or oil into the grease layer and then washing with soap and water.[18] It is known, therefore, that hydrocarbon oils are miscible with grease and hence easily penetrate grease and oil layers with the aid of some mechanical dispersion. If one then subjects these hydrocarbon oils to the action of concentrated sulfuric acid, one or more sulfonate groups, which are water soluble, are chemically added to the molecule, forming a sulfonated oil or petroleum. This molecule, which possesses an oil-soluble pole and a water-soluble pole, fulfills the basic requirements previously described for a typical detergent. At the same time, it preserves in its only slightly but significantly altered molecule the power to pentrate other grease or oil hydrocarbon layers. Thus, sulfonated petroleum (Sulfatate, Glyco) is used in most of the above mixtures, not only because of its own penetrating and detergent powers, but also as a vehicle or carrier for more powerful detergent substances. These latter otherwise might not be able to penetrate a grease layer except after considerable mechanical assistance in the form of massage. Again, once the detergents have been uniformly dispersed throughout the grease or oil, running water will wash both grease and detergent away. There is usually more attraction between detergent and the hydrophobic grease or particulate soil, so that the molecule of soil is literally dragged along with the attached detergent as the latter is carried away by the stream of water.[19]

For civilian use, in those burns contaminated only by light oils, ointments, or fats, usually applied by someone rendering first aid, almost any detergent mixture will prove efficient.

In military practice, however, burns are often covered with heavy fuel oil or grease, requiring more powerful cleansing mixtures which are easily dispersed throughout a heavy layer of these contaminating substances. While in burns sustained on land, fresh water is usually available to wash off oil-detergent combinations, in disasters at sea, salt water is the only water to be had in quantity. Detergent mixtures designed for the cleansing of burns on board ship must therefore possess

TABLE III

THE MOST EFFICIENT OF 100 DETERGENTS AND DETERGENT MIXTURES TESTED*

COMMERCIAL NAME	PROPORTIONS USED	CHEMICAL NATURE	ACTION	PHYSICAL NATURE OF MIXTURE
Sulfatate	9 parts	Sulfonated petroleum	Penetrant and detergent	Clear orange-yellow oil
Atlas—G 772 S (Atlas Powder Co.)	1 part	Sorbitan laurate	Emulsifier	Soluble in 3% NaCl
Sulfatate (Glyco Products Co.)	11 parts	Sulfonated petroleum	Penetrant and detergent	Clear, orange-yellow oil
Aerosol OT 25% aq. (Am. Cyanamid Co.)	1 part	Di-octyl sodium sulfosuccinate	Detergent	Soluble in 3% NaCl
Sulfatate	19 parts	Sulfonated petroleum	Penetrant and detergent	Clear, orange-yellow oil
Orvus (Procter & Gamble Co.)	1 part	A fatty alcohol sulfate	Detergent	Soluble in 3% NaCl
Sulfatate	49 parts	Sulfonated petroleum	Penetrant and detergent	Clear, yellow oil
Tergitol-4 (Carbon & Carbide Co.)	1 part	Higher secondary alkyl sodium sulfonate	Detergent	Soluble in 3% NaCl
Sulfatate	6 parts	Sulfonated petroleum	Penetrant and detergent	Clear, orange-yellow oil
Oil Turkey Red (Eimer & Amend)	5 parts	Sulfonated castor oil	Penetrant and detergent	Soluble in 3% NaCl
Aerosol OT 25% aq.	1 part	Di-octyl sodium sulfosuccinate	Detergent	
Oil Turkey Red	11 parts	Sulfonated petroleum	Penetrant and detergent	Thick, orange-yellow oil
Aerosol OT 25% aq.	1 part	Di-octyl sodium sulfosuccinate	Detergent	Soluble in 3% NaCl

*In all tests made on normal, intact skin, No. 6 fuel oil and also a very heavy grease (Permatex Water Pump Lubricant S-W, Permatex Co., Sheepshead Bay, N. Y.) were the final test substances.

the additional quality of solubility in sea water. Mixtures of various types are included in Table III. They all embody principles already discussed. Many other similarly patterned detergent mixtures are of course possible and are being investigated at this writing.

As outlined, the cleansing of a grease- or oil-covered burn is thus rendered as simple as possible. Penetration of the oily layer and union of detergent and oil molecules constitute the first step, and the non-traumatic washing away of grease and other superficial soil completes the cleansing procedure.

CLINICAL APPLICATION

Twenty-five patients with burns were treated in the Reception Ward of the Mount Sinai Hospital, New York City. All of these patients, who were ambulatory, sustained burns which were second degree in nature and involved a relatively small area of skin. In most instances, the burned areas, when first seen, were covered with ointments, fats, or oils, although an occasional area was contaminated with lubricating grease and considerable particulate matter. Several electrical burns of a superficial nature were coated with soot. During this period of study no burns were so extensive as to require hospital admission.

All burns covered with grease, oil, or fat were gently swabbed with cotton pledgets which had been soaked in a particular detergent mixture. No sedation was needed in these relatively minor burns. In many cases, only about two or three cubic centimeters of the mixture were necessary, and only a slight amount of swabbing was required to impregnate the grease or oil layer with the detergent (the heavier the type of grease, the greater was the amount of dispersing force needed). Sterile water was then allowed to flow over the burned area, with or without the gentlest of swabbing. The detergent and the contaminating agents were easily washed away in almost all instances, leaving a clean burned area. After gentle drying with a sterile towel, the burn was then ready for the débridement of vesicles and tanning. For evidence that all grease or oil had been completely removed, a good "take" of dye, usually a 2 per cent aqueous gentian violet, was attained at the first application. Dyed areas also seemed to show a tendency to dry more quickly, and areas usually difficult and slow to stain, such as débrided vesicles and other denuded portions, took up the dye as quickly or more quickly than the adjacent, easily coated areas.

The agents employed caused neither symptoms nor signs of local irritation or pain. Indeed, some of the preparations appeared even soothing in nature.

CONCLUSIONS

1. Most workers are of the opinion that vigorous cleansing methods have no place in the preliminary treatment of burns because (a) anes-

thesia is required, (b) shock is thereby increased, and (c) injury to remaining healthy tissue results from scrubbing and the use of irritating cleansing agents.

2. In many burns the tanning or coagulation method of local treatment would seem to possess the advantages of (a) simplicity of application, (b) prevention of fluid, electrolyte, and protein loss from the burned area, (c) prevention of subsequent exogenous infection, provided proper aftercare of the eschar is carried out, (d) rapid easing of pain, and (e) the facilitation of subsequent nursing and transportation. Infection arising from beneath the eschar speaks for the inadequacy of preliminary cleansing procedures. More recently, methods of treatment other than tanning have been recommended. These also have been discussed.

3. Certain of the synthetic detergents, employed in one of several combinations, act as cleansing agents in the local treatment of burns. Their unique properties which make them superior to other cleansing agents are (a) their ability to penetrate and "solubilize" substances such as greases, oils, and fats, as well as particulate matter; these types of contaminants are thus rendered more easily removable by water; (b) their lack of either irritating or noticeable tissue-damaging properties as employed; (c) their antiseptic nature; and (d) the fact that, after all grease, including the normal skin oils, is removed, the subsequent "take" of dye or tanning agent is rendered easier and a proper eschar more readily formed.

4. The principle of employing a penetrant detergent, such as sulfonated petroleum, as a carrier for other more powerful detergents is especially valuable, in so far as it greatly diminishes the amount of mechanical dispersion required to distribute the cleansing solution uniformly throughout an oil or grease layer.

5. In clinical tests with a number of detergent mixtures, performed both on controls with normal, intact skin, and on twenty-five patients with relatively mild, second degree burns, the properties listed above were substantiated. More than three-quarters of the burns when first observed in the emergency service of a metropolitan hospital were covered with grease, oil, fats, or ointments. It is in this group of cases, especially, that the action of the synthetic detergents is best demonstrated.

6. Burns covered with grease and oil, the result of military engagements on sea and land, represent a problem in which the application of these new cleansing agents may be of specific benefit.

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THE USE OF TANNIC ACID JELLY IN EXPERIMENTAL BURNS

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INTRODUCTION

THE importance of the proper emergency treatment of burns has been greatly accentuated by the marked increase in this type of injury in modern warfare. Military experience in the past two years has focused attention on the criticism made even before the present war, that tanning burned skin encouraged the spread of infection beneath the tanned area. It has also been emphasized recently that tanning is undesirable about the neck, face, and genitals and about joints where full range of motion might be limited by an inelastic eschar. In addition, tanning which completely surrounds an extremity may, of course, be dangerous because of constriction by an encircling eschar.

Tanning agents, however, have done a great deal to lower mortality and to alleviate pain during the first forty-eight hours following severe burns. Their use in first-aid treatment has had wide publicity among thousands of lay people, the services of whom must now be utilized in our medical defense program. Consequently, the indications for the use of such agents should be clarified and understood by civilian as well as military first-aid personnel.

It seemed wise, therefore, to investigate some of the properties of water-soluble tannic acid jelly, since this substance has been widely recommended in the first-aid treatment of burns of the trunk and extremities. This was attempted with the hope of learning under what circumstances such tanning may still be the procedure of choice.

Only the problem of the local first-aid treatment of the burn itself is considered. No attempt will be made in this paper to deal with the problems of shock, chemotherapy, and subsequent treatment of denuded areas.

Investigations were carried out on a 10 per cent tannic acid jelly in a water-soluble base, tragacanth, dispensed under the name of Tanaburn.*

MATERIAL AND RESULTS

The following studies were done:

1. Cultures of tanaburn, taken from unselected tubes of the jelly and planted on standard blood agar pour plates, showed no growth.

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*Manufactured by Tailby-Nason Co., Boston, Mass.

2. Standard blood agar pour plates were made incorporating tanaburn in approximately a 0.3 per cent solution, well dispersed in the liquid agar before the plates were poured. These were inoculated with pure cultures of (1) beta hemolytic streptococci, (2) *Staphlococcus aureus,* and (3) *Bacillus coli.* Control plates were poured with each of these organisms, leaving out the tanaburn. In each instance, the number of colonies present at the end of twenty-four and forty-eight hours in the tanaburn pour plates was equal to the number in the control plates.

3. A pure culture of beta hemolytic streptococci in dextrose broth was inoculated directly into tanaburn itself in a sterile test tube. This mixture was incubated and streak plates were made at six, twenty-four, and forty-eight hours. There was no growth in any of these preparations. It is probably not fair here to conclude that the tanaburn was bactericidal for the organisms in the absence of any media to support their growth.

4. The action of tanaburn on normal and infected burned skin when applied almost immediately after the burn was studied as follows: The chest and abdomen of an anesthetized dog were shaved. Standard burns were induced with an ordinary Bunsen burner flame, each area being exposed to the flame for approximately two minutes. This was sufficient to produce discoloration, blistering, and visible weeping of the burned area. At the conclusion of the experiment, the animal was sacrificed.

Four areas were burned as shown in Fig. 1 and treated as follows:

(a) Burned, infected with beta hemolytic streptococci, covered with a thick layer of tanaburn, and a dry sterile dressing applied

(b) Burned and covered with a dry sterile dressing

(c) Burned, infected as in (a) with beta hemolytic streptococci, and covered with a dry sterile dressing

(d) Burned, covered with a layer of tanaburn, and a dry sterile dressing applied (not infected).

Cultures were made by swabbing the skin surface and introducing the swab together with a small piece of skin, removed under aseptic precautions, into dextrose broth. The broth cultures were incubated two hours, and standard blood agar pour plates were made and examined at forty-eight hours. The results are shown in Table I. The cultures from the burned, infected, and tanned skin at one, three, five, and twelve hours, respectively, were saved, incubated forty-eight hours longer, and then streaked onto blood agar plates. The results are shown in Table II.

These experiments were then repeated on another animal, using boiling water burns and a different strain of hemolytic streptococci. Three areas were burned as illustrated in Fig. 2. Circulating boiling water was applied to the skin in each area for from one to two minutes, using

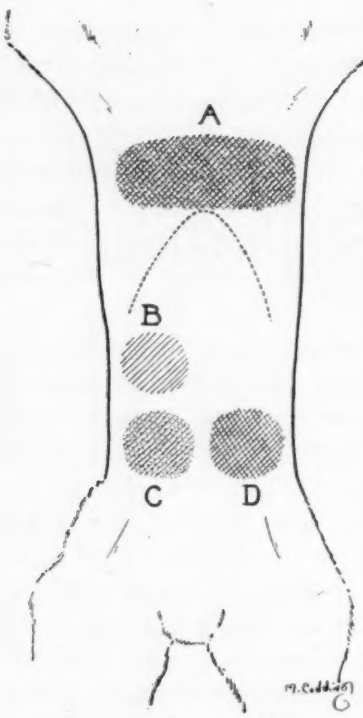

Fig. 1.

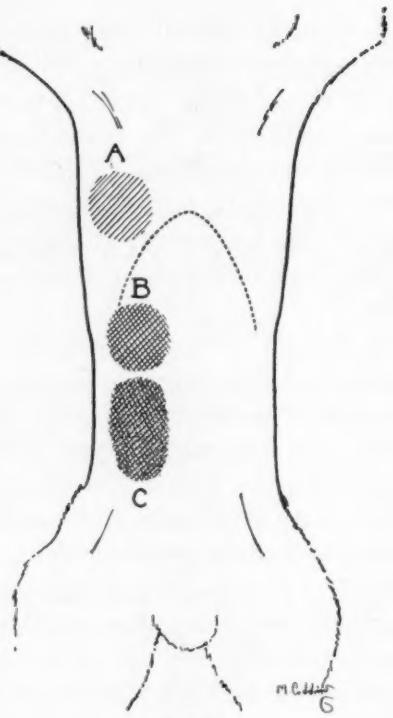

Fig. 2.

Fig. 1.—Experimental burns with Bunsen burner flame. *A*, Burned, infected, and tanned; *B*, burned; *C*, burned and infected; *D*, burned and tanned.

Fig. 2.—Experimental burns with boiling water. *A*, Burned; *B*, burned and tanned; *C*, burned, infected, and tanned.

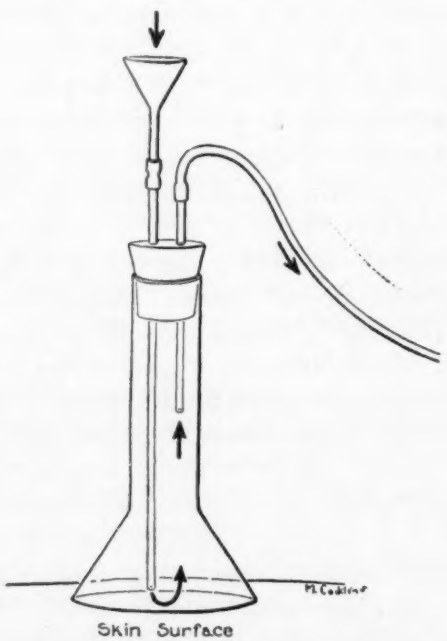

Fig. 3.—Device for applying circulating boiling water to annimal skin.

TABLE I

CULTURES AT 2 HR.	GROWTH AT 48 HR. (POUR PLATES)
1. Normal skin	1. Abundant growth of *Staphlococcus aureus* and *diphtheroids*
2. Burned skin at five hours each	2. No growth
3. Burned and tanned skin at five hours each	3. No growth
4. Burned and infected skin at five hours each	4. 25 to 30 colonies of beta hemolytic streptococci
5. Burned, infected, and tanned skin at one hour each	5. No growth
6. Burned, infected, and tanned skin at three hours each	6. No growth
7. Burned, infected, and tanned skin at five hours each	7. No growth
8. Burned, infected, and tanned skin at five hours each	8. No growth

TABLE II

CULTURES AT 48 HR.	GROWTH 48 HR. LATER (STREAK PLATE)
5. Burned, infected, and tanned skin at one hour each	5. No beta hemolytic streptococci
6. Burned, infected, and tanned skin at three hours each	6. 25 colonies of beta hemolytic streptococci
7. Burned, infected, and tanned skin at five hours each	7. Abundant growth of beta hemolytic streptococci
8. Burned, infected, and tanned skin at twelve hours each	8. Very abundant growth of beta hemolytic streptococci

TABLE III

CULTURES AT 2 HR.	GROWTH IN 48 HR. (POUR PLATES)
1. Burned skin at five hours each	1. No growth
2. Burned and tanned skin at five hours each	2. No growth
3. Burned, tanned, and infected skin at one hour each	3. No growth
4. Burned, tanned, and infected skin at three hours each	4. No growth
5. Burned, tanned, and infected skin at five hours each	5. 10 colonies of beta hemolytic streptococci
6. Burned, tanned, and infected skin at twelve hours each	6. 35 colonies of beta hemolytic streptococci

the device illustrated in Fig. 3. This was sufficient again to produce discoloration, vesiculation, and blistering of the skin. In this animal the areas were treated as follows:

(a) Burned and covered with a dry sterile dressing.

(b) Burned and covered with a layer of tanaburn and a dry sterile dressing (not infected).

(c) Burned, infected with beta hemolytic streptococci, and covered with a layer of tanaburn and a dry sterile dressing. Cultures of the burned skin similar to those made in the first experiment were made with results as shown in Table III.

Broth cultures in this instance were also kept, incubated forty-eight hours longer, and then streaked onto blood agar plates. The results are shown in Table IV.

TABLE IV

CULTURES AT 48 HR.	GROWTH 48 HR. LATER (STREAK PLATE)
3. Burned, tanned, and infected skin at one hour each	3. Few colonies of beta hemolytic streptococci
4. Burned, tanned, and infected skin at three hours each	4. Many colonies of beta hemolytic streptococci
5. Burned, tanned, and infected skin at five hours each	5. Abundant growth of beta hemolytic streptococci
6. Burned, tanned, and infected skin at twelve hours each	6. Very abundant growth of beta hemolytic streptococci

5. Observations were also made on the rate of formation of the eschar on these burned areas of skin. At the end of one and three hours after application of a thick layer of tanaburn, the eschar could be simply wiped or washed off with ease; at the end of five hours it could be washed off with some difficulty; and at the end of twelve hours a definite eschar had formed which could not be wiped off but had to be peeled off in a layer.

6. Microscopic sections stained with eosin and methylene blue were made of (1) burned, (2) burned and tanned, (3) burned and infected, and (4) burned, infected, and tanned skin all taken at five hours after burning and fixed immediately in Zenker's solution. All of these sections showed comparable amounts of subcutaneous edema. No distinction could be made microscopically between the tanned and the untanned burned skin. In none of the sections were microorganisms visible.

SUMMARY

1. Tanaburn, a 10 per cent tannic acid jelly in a water-soluble base, in itself is sterile.

2. A small amount of tanaburn exerted no bacteriostatic effect on pure cultures of beta hemolytic streptococci, *Staphylococcus aureus*, and *Bacillus coli* growing in blood agar media.

3. Beta hemolytic streptococci will not grow in tanaburn alone. This does not mean that tannic acid jelly is bactericidal but that it does not provide a media sufficient to support the growth of the organisms.

4. Beta hemolytic streptococci are readily recultured from burned and infected skin at the end of five hours. If this infected burn is covered with tanaburn, similar cultures taken at one, three, five, and twelve hours and incubated for two hours show no growth. However, if these cultures are allowed to incubate for forty-eight hours, then the three-, five-, and 12-hour cultures show increasing numbers of colonies of beta hemolytic streptococci. Tanaburn, therefore, is not bactericidal for these organisms, since they eventually grow out in profusion, but a definite bacteriostatic effect is evidenced by the absence of growth in the one- and three-hour cultures from both the flame and hot water burns.

5. Tanaburn begins to form an eschar on burned skin between three and five hours. This is quite thick, pliable, and cannot be washed or wiped from the skin at twelve hours.

6. Tanning the burned skin has no effect on the amount of subcutaneous edema present at the end of five hours.

COMMENT

These experiments seem to indicate that 10 per cent tannic acid jelly applied to infected burns of the skin exerts a transient bacteriostatic effect for periods up to three hours. However, after this length of time, bacterial growth proceeds readily. Also, after three to five hours an eschar forms which becomes more and more difficult to remove.

Burns covered immediately with a dry sterile dressing and burns which were tanned and then covered both remained sterile. Presumably the burn itself killed the organisms shown to be present on the normal skin control. It is during the period between the acquisition of the burn and the arrival of medical attention that the burn becomes infected—from surrounding skin, clothing, foreign bodies, and exposure to air contamination. In the laboratory this course of events was insured by actual inoculation of the burn with virulent organisms.

The ideal clinical first-aid local treatment of burns would consist in immediate application and maintenance of an adequate sterile and protective dressing until hospital care could be instituted. This is rarely possible, of course, outside of the experimental laboratory, and certainly not in the great majority of military or civilian wartime casualties. To condemn uniformly the tanning of burns is being idealistic. During war, the problems raised by individual lesions become secondary in importance to the adequate handling of a great volume of injuries. Under the conditions imposed by mass burning in crowded areas, the treatment must not only be efficacious, but also feasible.

Is there a place for tannic acid jelly in these circumstances? It is easy to apply. It has desirable analgesic properties. It is readily available. When satisfactorily employed, it forms a pliable, comfortable eschar which obviates the necessity for repeated painful dressings. However, its general use by the laity in large numbers of civilian or military casualties cannot be recommended without specific limitations. Although definite transient bacteriostatic properties appear to be present, 10 per cent tannic acid jelly is not bactericidal when used on infected burns. It is possible, therefore, that it may give the patient comfort and aid him physiologically through the first forty-eight hours after the burn, only to leave him with the subsequent severe complication of sepsis.

Experimental evidence indicates that tannic acid jelly should be used as a first-aid measure only when it can be applied almost immediately after the burn is incurred and only to burns which are not contaminated. In active, well-equipped first-aid stations near the scene

of a disaster this may occasionally be possible. Old and contaminated wounds should simply be covered with a sterile or the cleanest possible dressing and pain alleviated with large doses of sedatives until careful cleansing is possible. If the tannic acid jelly has already been applied to contaminated burns or to burns more than two hours old, then every effort should be made to remove it within three to five hours of the time of application, and local treatment suitable for any infected wound of this type should be carried out, supplemented, of course, by sulfonamide and supportive therapy.

THE EFFECTS OF THE APPLICATION OF A TOURNIQUET ON THE GENERAL RESPONSE TO GROSS TRAUMA TO AN EXTREMITY

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IN EXPERIMENTS[1, 2] recently performed in which a mechanical press was applied to an extremity for an extended period (fifteen hours), it was found that the animals succumbed even though plasma equal in quantity to that which was lost locally was administered intravenously. This was not the finding in a number of the experiments in which the press was applied for a shorter time (five hours). Since the pressure which was exerted on the tissues was the same in the two groups of experiments, the results indicated that the prolonged period of local ischemia and anemia was responsible for the difference in the severity of the general effects. In view of these observations in experiments on crush injuries, it was decided to study the effects of applying a tourniquet to an extremity after trauma to the soft parts had been produced. These experiments were compared with others in which a similar injury was caused, but no tourniquet was applied. In all the experiments, early death was prevented by the intravenous administration of blood plasma.

METHODS AND RESULTS

Large animals were used in all the experiments. Pain was prevented by the administration of nembutal and morphine. Trauma was produced by striking the soft parts of one of the posterior extremities many blows with a hammer. The number of blows varied somewhat according to the ease with which the muscular tissue became damaged. The usual time required for the carrying out of the trauma was about four minutes. The femur was not fractured and an attempt was made not to cause a break in the skin.

Ten animals served as controls, no tourniquet being used. In the remaining ten animals a rubber tourniquet was applied tightly around the upper part of the thigh, proximal to the upper level of the trauma, as soon as the infliction of trauma was terminated. An attempt was made to exclude the arterial inflow as well as the venous return of the extremity. The period that the tourniquet was left in place was five hours.

In the control experiments blood plasma was administered intravenously two hours after the traumatization of the extremity. The rate

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of injection was equivalent to 1 per cent of the body weight of the recipient per hour. In the experiments in which a tourniquet was used, the injection of plasma was begun simultaneously with the removal of the tourniquet. The arterial blood pressure was essentially normal at the time.

The quantity of plasma that was given in most experiments equalled 5 per cent of the total body weight of the recipient. This figure was chosen because it was found in earlier experiments by one of us[3] and by Parsons and Phemister[4] that this type and degree of trauma result in the regional loss of fluid (mainly whole blood) equal to approximately 5 per cent of the body weight, which is about one-half of the total blood volume. In some of the experiments in which a tourniquet was applied, the amount of fluid which was given was greater.

The various studies which were performed included the arterial blood pressure, the hematocrit reading, the pulse rate, the plasma creatine and creatinine, the urinary creatine and creatinine, the nonprotein nitrogen, and gross and microscopic examinations of the urine. The methods which were employed have been enumerated previously.[1]

The animals were observed until death or recovery took place. If death occurred, the local loss of fluid into and near the injured area was determined by the bisection method[3] that has been described previously.

As has been stated, ten control experiments were performed. The extremity was traumatized but no tourniquet was applied. Eight of the ten animals recovered, one animal dying at the end of ninety hours and the other on the twelfth day. Previous experience[3] with this method of producing injury would indicate that most of the animals would have died had plasma not been injected. Examination of the animal which died at ninety hours showed bilateral pneumonia and an abscess of the thigh. The animal which died on the twelfth day also had an abscess of the thigh. Some of the results of these experiments are given in Table I.

Alterations which were observed in the first ten hours following the traumatization of the control animals included an elevation in the pulse rate and a decrease in the hematocrit reading. The latter alteration was probably due, mainly, to the injected plasma. There was very little alteration in the arterial blood pressure, the plasma creatine, and the nonprotein nitrogen. In some instances the traumatization was followed by a slightly reddish discoloration of the urine and by the presence of a few erythrocytes and granular casts in the urine.

The findings in the ten experiments in which a tourniquet was used differed from the controls in a number of respects. All the animals died, the survival period following the removal of the tourniquet varying from three to thirty-six hours, the average being approximately fourteen hours. Five of the ten animals were given plasma in an amount which equalled 9 per cent or more of the body weight of the recipient

TABLE I

SHOWING THE EFFECTS OF TRAUMA TO AN EXTREMITY AND OF PLASMA THERAPY (NO TOURNIQUET)

EXPERIMENT NO.	ARTERIAL PRESSURE (MM. HG)		HEMATOCRIT READING		PULSE RATE PER MIN.		THERAPY PLASMA PER CENT BODY WEIGHT	RESULT
	CONTROL	6-8 HR. AFTER PLASMA BEGUN	CONTROL	6-8 HR. AFTER PLASMA BEGUN	CONTROL	6-8 HR. AFTER PLASMA BEGUN		
1	120	105	46.3	32.7	124	184	5	Died on twelfth day
2	115	125	55.4	32.0	140	194	5	Recovered
3	115	105	53.8	45.0	116	180	5	Recovered
4	110	115	56.0	34.0	136	160	5	Recovered
5	115	120	52.0	39.5	96	220	5	Recovered
6	120	100	56.6	39.0	112	194	5	Recovered
7	120	120	53.6	24.0	140	196	5	Recovered
8	115	115	41.7	29.5	116	192	5	Died after 90 hours
9	115	95	55.0	38.3	92	200+	5	Recovered
10	110	120	50.2	39.0	104	180	5	Recovered

instead of the usual 5 per cent. The survival period did not appear to be lengthened by the administration of the larger quantity of plasma. The average amount of plasma injected in the ten experiments equalled 7.3 per cent of the body weight of the recipient and the average regional loss of fluid equalled 7.8 per cent of the body weight. This shows very clearly that the regional loss of fluid in experiments of this type in which a tourniquet and replacement therapy were used was not responsible for the uniformly fatal results. Some of the results are given in Table II.

Whereas no significant decline in the arterial pressure occurred in the control experiments, a marked decline was found following the removal of the tourniquet in the experiments in which the constriction was used. This occurred despite the fact that the plasma was introduced at a rather rapid rate in some of the experiments. There was an acceleration of the pulse rate and a decline in the hematocrit reading. In contrast to the observations in the control experiments, the plasma creatine and the non-protein nitrogen became elevated. The urine became darker in color and a moderate number of erythrocytes and granular casts were seen on microscopic examination.

DISCUSSION

An attempt was made to cause the same amount of injury to tissues in all of the experiments. The fact that death occurred in all the experiments in which a tourniquet was applied to the injured extremity, whereas eight of the ten control animals survived, appears to be of significance. The survival period of the two control animals which died was longer than that of any of the animals in the other group. The results show very clearly that the prolonged application of a tourniquet to an injured extremity results in harmful effects.

TABLE II

SHOWING THE EFFECTS OF TRAUMA TO AN EXTREMITY, OF THE APPLICATION OF A TOURNIQUET, AND OF PLASMA THERAPY

EXPERIMENT NO.	ARTERIAL PRESSURE MM. HG		HEMATOCRIT READING		PULSE RATE PER MIN.		HOURS TOURNIQUET APPLIED	THERAPY PLASMA PER CENT BODY WEIGHT	SURVIVAL AFTER TOURNIQUET REMOVED (HR.)	FLUID LOSS PER CENT BODY WEIGHT (REGIONAL)
	CONTROL	4-6 HR. AFTER TOURNIQUET REMOVED	CONTROL	4-6 HR. AFTER TOURNIQUET REMOVED	CONTROL	4-6 HR. AFTER TOURNIQUET REMOVED				
1	115	50	52.3	39.8	144	200±	5	9.2	13	8.31
2	125	60	55.8	50.8	136	200+	5	10.4	26	11.63
3	115	80	41.2	27.0	160	186	5	10.0	13	9.59
4	120	0	38.0	36.4	140	140	5	9.8	3	5.32
5	130	80	53.2	30.3	146	200+	5	9.0	6	9.14
6	110	50	38.3	27.4	108	200+	5	5.0	14	5.15
7	105	75	36.4	30.0	148	164	5	5.0	36	4.58
8	120	70	53.0	41.8	124	200+	5	5.0	13	8.68
9	110	70	38.3	34.0	128	184	5	5.0	14	7.91
10	115	45			136	200+	5	5.0	5.5	9.36

The findings recorded here receive support from previous experimental and clinical observations. A number of observers have produced shock by interfering with the circulation to a large portion of the body for a considerable time. Wilson and Roome[5] found that the removal of a tourniquet is followed by the passage of a large amount of the blood volume into the dilated blood vessels of the extremity. As a result of clinical observations and reports in World War I, Cannon[6] stressed the dangers of the removal of a tourniquet which had been in place for hours.

It is obvious because of the present and of the previous studies that a tourniquet should be used for the control of bleeding only if other means are not available or will not suffice. If the extremity is badly damaged and if a tourniquet has been in place for several hours when the patient reaches a point where definitive treatment may be employed, amputation is usually advisable. Our previous experiments on crush injuries, as well as the observations of Allen[7] and of Brooks and Duncan,[8] indicate that the harmful effects of a tourniquet will be lessened if the temperature of the part distal to the constriction is lowered by the application of ice. Unfortunately, under emergency conditions, means for lowering the temperature are not usually available.

SUMMARY

Experimental findings are presented which show that the prolonged application of a tourniquet to an injured extremity greatly lessens the chances of survival of the animal.

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GRADUAL OCCLUSION OF THE MESENTERIC VESSELS

Experimental Study

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WHEN a thrombus forms very slowly, collateral circulation has an opportunity to carry the blood supply. Warren and Eberhard[15] have pointed out that a very gradual occlusion of the main mesenteric vessel may, in some instances, result in infarction of the intestine; in other instances there may be temporary symptoms of pain and intestinal hemorrhage; it may even result in no symptoms at all if it forms slowly enough. Narrowing of the mesenteric vessels is not uncommon as a feature of generalized arteriosclerosis.

There have been occasional cases reported in which the main artery was slowly occluded, causing no untoward symptoms during life and no involvement of the intestine at autopsy. Best known of such cases are those of McCallum,[1] Trotter,[2] and Howse.[3]

Councilman,[4] Reich,[5] Davis,[6] Garcia,[7] and Moore[8] reported cases in which the collateral circulation after mesenteric occlusion was sufficient to prevent pathologic changes in the bowel wall, but not sufficient to allow normal function to continue. Intestinal ileus results in such cases. In Moore's case the patient suffered from intestinal obstruction due to a localized area of paralytic ileus caused by occlusion of mesenteric vessels. The blood supply was sufficient to keep the bowel alive, but could not sustain normal function. Following a lateral anastomosis the patient made a complete recovery.

Karcher[9] reported a case in which surgical treatment was not undertaken despite typical symptoms of mesenteric vascular occlusion, because of the poor condition of the patient. In other instances, lack of diagnosis or just watchful waiting with general support of therapy have resulted in a spontaneous recovery. Karcher's patient died from another cause seven weeks after the occlusion had taken place. An autopsy revealed an embolus completely occluding the superior mesenteric artery. The bowel was not infarcted.

Experimental reproduction of a long-term gradual occlusion of the main mesenteric vessels has not, to my knowledge, been previously reported. It is, therefore, of some interest to report the experimental results of such occlusions.

Pearce[10] has recently advocated the use of cellophane for the experimental gradual occlusion of large arteries. Mims Gage[11] has reported

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the experimental production of hypertension by encasing the kidney of a dog in cellophane and allowing it to become constricted over a long period of time.

We have been able to completely occlude the superior mesenteric artery by gradual constriction over a period of four months by the use of cellophane in three of six animals in which this procedure was carried out. A similar procedure, constricting the superior mesenteric vein, was successfully accomplished in two of five attempts.

EXPERIMENTAL DATA

Ordinary DuPont cellophane No. 300 P.T. was used. It was soaked in phenol for ten minutes and then alcohol for about one hour before operation. A ¼-inch wide strip consisting of four folded layers was loosely wrapped about the vessel. The ends were sutured with a silk mattress stitch so that the cellophane hugged the vessel snugly, but did not constrict. The animals were allowed to continue normal existence for four to five months, at which time they were opened for examination. It was noted that the animals in which the superior mesenteric artery was so treated became progressively thinner and lost their appetites. Those animals in which the superior mesenteric vein was wrapped with cellophane at no time showed any ill effects.

Observations.—In three of the six animals in which the superior mesenteric artery was wrapped with cellophane, it was found that the artery had become completely occluded over the course of sixteen to

TABLE I

GRADUAL OCCLUSION OF MAIN MESENTERIC VESSELS BY CELLOPHANE

	DATE CELLOPHANE APPLIED	DOG NO.	DATE OF LAPAROTOMY OR SACRIFICE OF ANIMAL	FINDINGS
Arterial	11/14/40	1C	3/18/41	Occlusion not complete
	12/18/40	4C	4/21/41	Occlusion complete; low grade enteritis; thrombosis of small vessels
	1/ 8/41	5C	5/20/41	Occlusion not complete
	1/15/41	7C	6/10/41	Occlusion not complete
	1/15/41	8C	6/10/41	Occlusion complete; enteritis; erosion of mucosa
	11/22/41	9C	6/10/41	Occlusion complete
Venous	11/27/40	2C	3/18/41	Occlusion not complete
	12/18/40	3C	4/21/41	Occlusion not complete
	1/ 8/41	6C	5/20/41	Occlusion not complete
	11/11/41	10C	3/23/42	Occlusion complete
	11/11/41	11C	3/23/42	Occlusion complete

eighteen weeks. In the remaining three animals complete occlusion had not yet taken place. The cellophane had produced a severe degree of tissue irritation, causing extensive changes around the vessel. These changes consisted of a fibroplastic response with purulent or gelatinous fluid encased about the cellophane. The intestinal wall appeared very pale and thin in these animals. Microscopic examination of the intestinal

wall revealed a low-grade enteritis of varying degree in the various specimens, with erosion of the villi and leucocytic infiltration of the remaining mucosa and submucosa. There was no infarction present. However, the small subserosal vessels contained thrombi (Fig. 1). The similarity of the results in the three animals indicated that the lesion in the intestine was directly the result of the gradual occlusion of the superior mesenteric artery. No changes were noted in the intestinal walls of the dogs in which the occlusion was incomplete. Blood pressure readings were not taken.

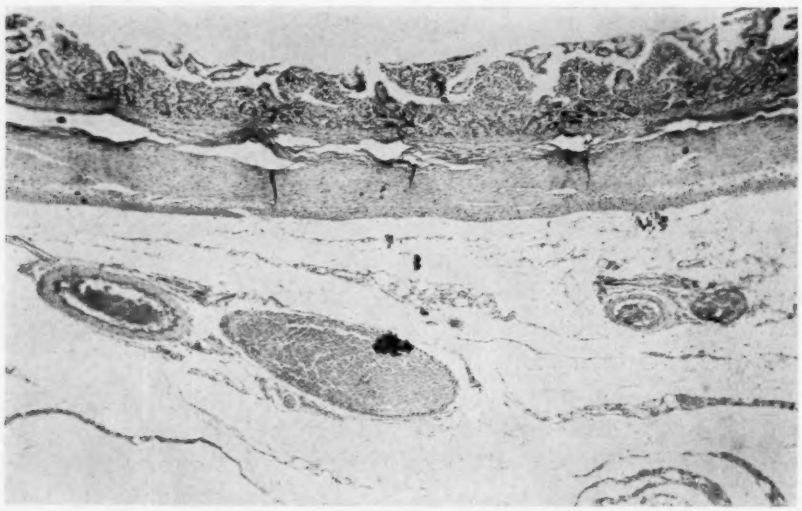

Fig. 1.—Microscopic appearance of small intestine after gradually induced, complete occlusion of the superior mesenteric artery in the dog by cellophane after approximately four months. Note erosion of mucosa, infiltration by polymorphonuclear leucocytes (low-grade enteritis), and thrombosis of small subserosal and intramural vessels. Grossly the intestine appeared markedly anemic with thinned out walls.

It is known that blockage of the lymph channels of the mesentery can produce an ulcerative lesion in the intestine, the microscopic appearance of which is not dissimilar from that described above (Poppe[12]). It is thus possible that the irritative response produced by cellophane may have blocked the lymph channels as well as the arterial supply. Thus, the lesion produced may be the result of either or both, chronic hypoxia and chronic infection with lymphatic blockage.

Gradual occlusion of the superior mesenteric vein resulted in no lesion of the intestine in either of the two animals successfully ligated. However, it was interesting to trace the collateral venous drainage of the intestine, especially since there was no embarrassment of the intestinal circulation. Preparations were made, therefore, for roentgen-ray study by injecting a dilute solution of barium sulfate into one of the small mesenteric veins. The accompanying roentgenogram illustrates the remarkable collateral circulation established as a result of the gradual occlusion. Adhesions were found between the fibroplastic mass around the cellophane and loops of intestine, the omentum, and portion of mesentery. The collateral blood channels established in these adhesions

are well shown in the photographs. An interesting source for collateral circulation was noted in small vessels which apparently traversed the posterior parietal peritoneum and found their way into the kidney (Fig. 2).

The abundance of the collateral supply explains the paucity of symptoms and the absence of circulatory changes associated with the long-

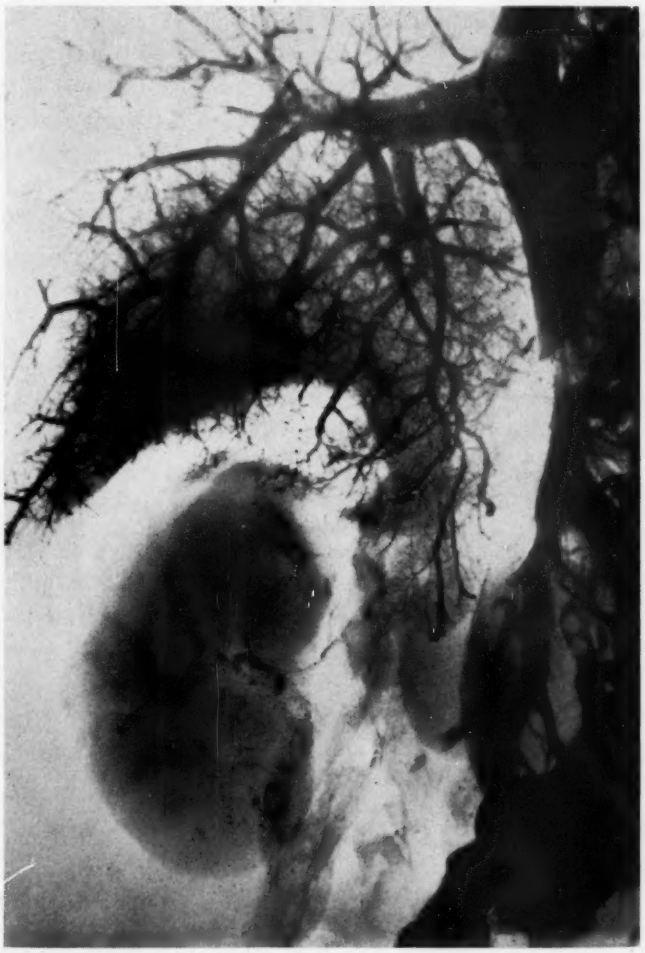

Fig. 2.—Result of gradually induced, complete occlusion of the superior mesenteric vein in the dog by cellophane after approximately four months. Illustration shows roentgenogram of specimen injected with dilute barium sulfate solution. The venous tree of the liver (above) received blood from collateral channels which formed about the occlusion. Collateral channels are also shown in the posterior parietal peritoneum and capsule of the kidney. Not shown are further collateral channels found in numerous omental adhesions about the occlusion.

term type of gradual occlusion of the superior mesenteric vein. Twenty cases illustrating this type of total occlusion in man as an incidental necropsy finding associated with no intestinal changes were reported by Laufman and Scheinberg.[13]

Felsen[14] has presented clinical and autopsy material illustrating the effects of long-term anoxia due to intestinal vascular sclerosis. He describes a proliferative phase and an obliterative phase in the intra-

mural vessels resulting from gradual occlusion of the mesenteric vessels. In the proliferative phase the intramural vessels are thickened and tortuous, while in the subsequent obliterative phase these capillaries are straightened and rigid, with obliterated terminal arborizations. The experimental observations presented above apparently are commensurate with the obliterative phase with superimposed low-grade inflammation.

SUMMARY

Gradual occlusion of the superior mesenteric vessels over a period of four to five months was accomplished in dogs by the use of cellophane bands. Complete occlusion of the superior mesenteric artery was accomplished in two of five attempts. In the remaining animals the vessels were constricted but not completely occluded.

The result of gradual complete occlusion of the superior mesenteric artery was an anemia of the intestinal wall with a superimposed low-grade enteritis. Thrombi were present in the intramural vessels.

Gradual complete occlusion of the superior mesenteric vein resulted in no demonstrable lesion in the intestine. Extensive collateral circulation was established in these animals, including the vascularization of omental adhesions and of the posterior parietal peritoneum.

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INJECTION OF VARICOSE VEINS

The Importance and Technique of Injecting the Elevated Extremity

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INTRODUCTION

With the perfection of sclerosing therapy for varicose veins of the lower extremities, surgeons in general have come to avail themselves of this method of varicose vein therapy. McPheeters'[1] writings on the ambulatory injection treatment of varicose veins served to stimulate considerable interest in this mode of management in this country. Since, probably, about 10 per cent of young healthy adults suffer from varicose veins, and since most of these people are engaged in activities which necessitate a minimum of medical care during the treatment, any method which would reduce the number of required injections would be an approach to the ideal injection technique. Everyone who has acquainted himself with the injection technique has come to realize that the necessity of giving as many as twenty injections in those cases in which there are numerous varicose radicals of the main varicose trunk is not an inviting feature to patients. If a method could be found by which the number of injections could be reduced to one or two, a big disadvantage would be overcome. The purpose of this communication is to describe such a method.

Generally, the principle embodied in the obliterative treatment is to maintain the sclerosant in contact with the intima of the vein long enough to produce an intimal inflammation eventuating in thrombus formation and, finally, fibrosis. In the usual method, the varix is injected with the patient in the horizontal or sitting position, several injections being made at different sites at one visit, or single injections being given at successively lower levels at successive visits. Fig. 1*A* diagrammatically illustrates such an injection. The sclerosant, injected into an engorged vein, does not diffuse, coagulation of the immediately surrounding blood further impeding the spread of the solution. This results in a localized thrombus which can be felt later as a hard, fibrotic lump. Attempts to inject a segment after "stripping" it of its

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blood are often discouraging, since incompetent communicating veins allow the inflow of blood.

The method described in this communication has been employed successfully in a large series of cases on the Surgical Service of the O'Reilly General Hospital, U. S. Army, Springfield, Mo., and in the Surgical Outpatient Clinic of the University of Minnesota Hospital, Minneapolis. With this simple technique, almost all patients have required a single injection, while a few have been given two injections. The effectiveness of this method lies in the principle that a relatively small amount of sclerosant—a few cubic centimeters—when injected into bloodless veins, reduced to capillary spaces, can produce intimal inflammation in all the varices of an extensively varicosed venous circulation. The sclerosant is undiluted by blood, and, theoretically, 1 c.c. should be sufficient to sclerose many yards of such collapsed veins.

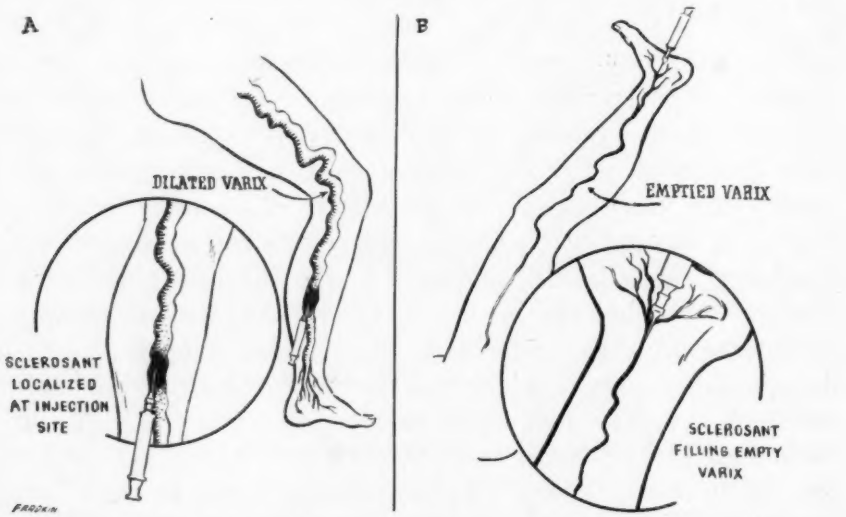

Fig. 1.—The effect of position of the extremity on diffusion of sclerosing solution injected into a varix. *A*, Extremity dependent, showing localization of sclerosant in varix dilated with blood. The final thrombus develops at the site of injection only. *B*, Extremity elevated, showing sclerosant flowing through capillary lumen of collapsed varix. The final thrombus develops in the entire vein.

INDICATIONS

Before proceeding with varicose vein therapy, certain contraindications must be observed,[2] among which are the following:

A. Systemic diseases
- Malignancy
- Angina pectoris
- Cerebral thrombosis
- Myocardial disease
- Hyperthyroidism
- Active tuberculosis
- Acute infectious diseases (including acute upper respiratory infections and tonsillitis)

B. Local conditions
Lack of patency in the deep venous system
Impairment of arterial circulation
Inflammation or infection of the deep or superficial venous system

Schwartz's test (palpation of a varix below the knee while percussing the saphenous vein in the upper part of the thigh) is positive if an impulse can be palpated below. This indicates incompetence of the valves between the site of palpation and the site of percussion and is always positive in varices of the great saphenous system. The incompetence of the saphenous valves may be verified by the Trendelenburg test. This is performed simply by elevating the affected extremity for a few minutes and then compressing the saphenofemoral junction, while the patient is allowed to stand. If the veins of the leg fill rapidly (within thirty seconds), incompetence of the valves in the communicating veins may be assumed. If a slow filling occurs (over thirty seconds), the communicating system is relatively uninvolved. It may be recalled that there are from one to three communicating veins in the thigh and from fifteen to thirty in the leg. Should additional dilatation of the saphenous system take place when the digital compression of the saphenofemoral junction is removed, one may assume that back pressure in the venous column from the heart to the varix contributes to the vicious cycle.

If the Schwartz and Trendelenburg tests are positive, high interruption of the saphenous vein at the saphenofemoral junction is indicated, providing the deep system is patent. A simple test for patency of the deep venous system is the tolerance, for a few hours, of an elastic bandage wrapped snugly from the ankle to the lower thigh. Perthes' test may also be performed for this purpose. In this test, a tourniquet to compress the superficial veins is placed above the varices and the patient allowed to walk or vigorously exercise the knee. If the varices become more prominent, the deep veins are probably obstructed (negative Perthes' test); if the varices collapse or become less prominent, the deep veins are patent (positive Perthes' test). Mahorner and Ochsner[3] have described a refined segmental Perthes' test.

If high saphenous interruption is found to be indicated, it should be performed before sclerosing therapy is instituted, since back pressure from above will nullify the results expected from even perfect injection technique. The widely accepted operative procedure described by de Takáts[4] carries a 0.3 per cent risk of pulmonary embolism (Faxon and Barrow[5]), but ligation alone will cure about 20 per cent of the patients, the remaining 80 per cent requiring sclerosing injections.

METHOD

With the patient sitting on the table and the lower extremities on a nearby stool or simply flexed over the side, one of the most distal varicose veins, one usually around the ankle, is selected. A No. 25

gauge needle to which is attached a syringe containing 3 to 5 c.c. of a sclerosing solution is inserted into the vein at the most convenient distal point. With the syringe held firmly in place, but without injecting any of the sclerosant, the patient's lower extremities are brought carefully onto the table; the patient lies horizontally, and the affected extremity is elevated by an assistant to at least 45° with the horizontal (Fig. 1*B*). As much as possible of the blood contained in the veins is permitted to drain into the deep system, and when the extremity appears pale, the sclerosant is injected into the ankle vein and the needle removed. No bleeding occurs from the needle puncture since the point of injection is elevated above the level of venous pressure. A small dry dressing is placed over the puncture site and an elastic bandage wrapped from the ankle to the middle of the thigh. The extremity is then placed on several pillows and the patient allowed to remain in that position for twenty minutes, following which the patient is allowed to be ambulatory. The importance of walking about after this postinjection period has been stressed by Dean and Dulin[6] as a prophylactic against embolism.

Any of the popular sclerosants may be employed. Monoethanolamine oleate (monolate) is an effective agent and causes no slough if perivenous injection takes place (Glasser,[7] Meyer[8]). We have used 5 per cent sodium psylliate (sylnasol), which Biegeleisen[9] showed has a remarkably low toxicity, with equal success. Quinine hydrochloride and urethane has also been found to be an excellent sclerosant.

COMMENT

Injection of the sclerosant into the collapsed varix permits a relatively undiluted solution to remain in contact with the intima during the period of elevation of the extremity. The surplus solution flows into the deep venous system where it is diluted and rendered ineffective as a sclerosant. The period of twenty minutes in which the extremity remains elevated and the veins collapsed is sufficient to initiate an intimal reaction which proceeds to thrombosis and, finally, fibrosis. In nearly all of our patients, a single injection has been sufficient; a few patients have required two injections, the second being into a functionally independent varicose system; no patient has required more than two injections for complete thrombosis. If recurrence after sclerosing therapy is due to incomplete injection, the technique suggested in this paper should minimize this possibility.

With the method suggested here there is an appreciably greater periphlebitis produced parallel to the greater venous length which is inflamed and thrombosed. This pain can be adequately controlled with the usual analgesics such as aspirin, phenacetin, or small doses of codeine.

SUMMARY

A successful method of sclerosing varicose veins by the injection method is described. With this technique the sclerosant is injected into relatively bloodless veins. Usually, it has been possible to produce thrombosis of the entire varicose system by a single injection of sclerosant.

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"CYLINDROMA" (ADENOCARCINOMA, CYLINDROMA TYPE)

Report of Two Cases With Metastasis

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In a recent review of primary tumors of the submaxillary gland[2] we called attention to the frequent incidence, in this location, of a type of neoplasm termed "cylindroma." It was found that throughout the literature in general, and in many of the older cases of our own series in particular, this neoplasm was confused frequently with "mixed tumor." It was observed, in our series, that these cylindromas (adenocarcinomas of cylindroma type) were associated with an extremely high incidence of recurrence, even after radical operative procedures. Infiltrative tendencies were most pronounced with special reference to perineural lymphatic involvement. Metastasis was not infrequent and the prognosis, in general, proved unfavorable not only in those instances in which the neoplasm was a pure cylindroma but also in our small group of examples showing transition to the mixed tumor type.

During preparation of the aforementioned review two additional examples of "cylindromas" came under our observation. In one case the tumor had its origin in the tongue; in the other the primary site could not be ascertained with certainty, but the parotid gland appeared to be the probable source. In reporting these two cases it is not our purpose to review the literature or to enter into controversies regarding histogenesis. Our wish is merely to reemphasize the dangerous potentialities of this particular type of malignant process and the importance of distinguishing it from the ordinary mixed type tumors which have a vastly different prognosis.

REPORT OF CASES

Case 1.—A married white man, 35 years old, first registered at the Mayo Clinic on June 17, 1939, complaining of pain in the right ear of four years' duration. The family and personal histories were irrelevant. Previous operations had included appendectomy in 1922 and tonsillectomy in 1938. The condition of which the patient complained had begun rather insidiously, with intermittent pain in the right ear, in 1935. Just prior to the onset of pain the patient had been swimming much and to this he had attributed his trouble. The pain continued, however, and became constant in character. Usually it was a dull ache, but as time went on, sharp exacerbations began to occur at irregular intervals. Tonsillectomy had been performed but had given him practically no relief from symptoms. During the year prior to his admission, soreness had developed in the right side of the throat. At about this time the patient observed that chewing aggravated the pain in his right ear. He complained of nothing else except mild dyspepsia of some years' duration. Extensive

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studies made at that time revealed nothing more serious than granular pharyngitis and a healing duodenal ulcer. The pain in the ear was considered to be on the basis of glossopharyngeal neuralgia. The patient was dismissed with instructions to follow a regime for ambulatory patients with ulcer.

The patient was next seen at the clinic on June 18, 1941. The pain in the right ear and the soreness in the right side of the throat had persisted, with increased severity, the pain sometimes awakening the patient at night. Recently there had developed a "paralyzed feeling" in his throat, with some difficulty in swallowing and articulating. He also stated that food particles seemed to lodge at the base of his tongue, on the right side.

Examination disclosed an indurated, submucous nodule on the right side of the tongue, near the base. This nodule was fixed superficially and deeply, and was considered to be malignant. One of the upper deep cervical lymph nodes was enlarged and somewhat firm, suggesting the probability of metastatic involvement. The results of general physical examination were otherwise negative except for a questionable enlargement of the liver. Roentgenograms demonstrated a persistence of a duodenal deformity characteristic of ulcer.

At operation on June 25, 1941, the tumor of the tongue was found to be too extensive for surgical removal. Biopsy was therefore done and fourteen radon seeds were inserted. Seven radon seeds also were inserted into the substance of the enlarged right cervical lymph node which had been ascertained, at the time of operation, to be malignant.

The patient made two subsequent visits to the clinic. On the first of these, August 18, 1941, reduction was noted in the size of the primary lesion of the tongue and of the metastatic nodule in the cervical region. On his last admission, Oct. 11, 1941, the patient complained of pain and tenderness in the right side of the upper part of the abdomen. This pain had some features suggestive of cholecystitis with stones and, on one occasion, had necessitated the use of opiates for relief. It was described as a persistent dull ache with frequent exacerbations of increased severity. Loss of strength and appetite were noted, but not jaundice or fever. Chilly sensations had accompanied one of the attacks of pain.

Examination of the head and neck revealed marked reduction in the size of the primary neoplasm, as well as in that of the metastatic nodule. Opinions regarding the condition of the abdomen were best summarized in the consultant's note: "Tender, nodular, enlarged liver with constant pain past six weeks. Severe attack seven days ago requiring opiates for relief. Considerable loss of strength and weight. Impresses me as metastatic carcinoma of the liver (source ?). Believe exploration warranted because of youth and good general condition of patient."

On Oct. 14, 1941, surgical exploration of the abdomen was carried out through a small right rectus incision. The liver was found "to be full of metastatic (tumor) nodules." A small specimen for biopsy was taken from one of these nodules to determine the primary source of the malignancy. Because of the utter hopelessness of the patient's condition no further roentgen therapy was advised. He was dismissed from our care on Oct. 22, 1941.

Pathologic Aspects.—Material for study consisted of two small nodules removed at biopsy from the tongue and liver, respectively. These nodules were grayish brown and of rather firm consistency. There was nothing on gross examination, however, to suggest the exact nature of the pathologic process involved. Study of microscopic sections prepared from both lesions presented pictures so similar as to enable one to write a single pathologic description. Under the low-power objective one was struck by the cellularity and manifestly malignant properties of the lesion. In neither instance could the invaded tissue (lingual muscles and hepatic parenchyma) be identified. In both lesions a characteristic arrangement of tumor cells was seen, with a grouping in the form of plugs or cylinders, many of which contained hollow centers

(Fig. 1*a* and *b*). Under the higher power objectives of the microscope the tumor cells were seen to be small and deeply stained with hematoxylin. Size was remarkably uniform and cytoplasm was scanty in amount and ill defined in outline. The nuclei were relatively large, and very hyperchromatic, yet mitosis was rarely encountered. The cystic areas observed were seen to represent attempts at the formation of acini and alveoli, and the entire picture appeared to be compatible with a diagnosis of grade 1 adenocarcinoma (Broders), cylindroma type. Hyaline stromal changes so typical of cylindroma were noted.

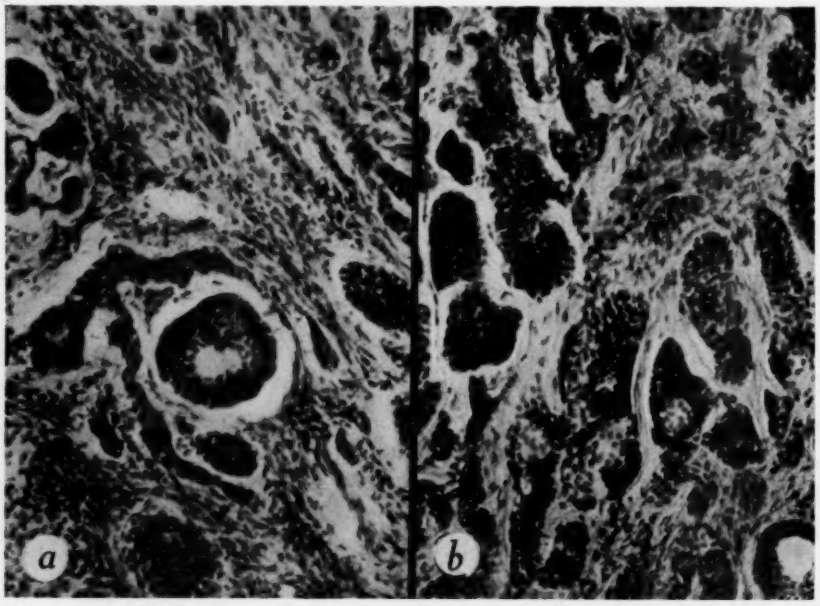

Fig. 1.—*a*, Primary lesion of the tongue, showing strands and solid and cystic cords of cylinders of small hyperchromatic tumor cells (hematoxylin and eosin ×135); *b*, adenocarcinoma, grade 1, cylindroma type, from one of the metastatic nodules in the liver (hematoxylin and eosin ×135).

CASE 2.—A married white woman, 48 years old, first registered at the clinic on June 14, 1938, complaining of pain in the right ear, of nine years' duration. Her family history and past medical record had been irrelevant. The patient's husband and three children were living and well. Her present illness had begun nine years prior to registration, with intermittent pain in the region of the right ear. This pain continued, and when medical advice was sought a small tumor was discovered and removed. The pathologic report at that time was adenocarcinoma, probably of sebaceous glandular origin, and the patient was treated with a total of 5400 milligram hours of radium with a view to preventing recurrence. Temporary control was obtained, but pain returned.

Examination at the clinic disclosed what appeared to be a recurrence of a malignant process filling the right external auditory canal. Extension was apparent in the upper and inner aspect of the auricle. Postauricular tenderness was elicited. Roentgenograms of the right mastoid region revealed a diffuse cloudiness, with no actual evidence of destruction of bone.

At operation on June 15, 1938, an extensively recurrent neoplasm was found involving the entire external auditory meatus. The inner and upper surfaces of the auricle were involved and there was extension into the skin of the preauricular and postauricular regions. Deeply, involvement of the right mastoid process was apparent. An extensive operation, including mastoidectomy and removal of the vesicles,

was performed in an effort to eradicate the neoplastic tissue, which proved to be grade 2 adenocarcinoma of the cylindroma type. Postoperatively, intensive roentgen therapy was administered. The patient returned on four occasions for further observations and continuance of roentgen therapy. On her fourth admission (July 5, 1939), she complained of preauricular tenderness and a nodule in the mastoid region. Examination disclosed several zones of apparently recurrent neoplastic tissue in the preauricular and postauricular areas. These were treated by excision (cautery). Needles containing radium were inserted locally. Microscopically, the nodules of tissue removed again were typical of adenocarcinoma of the cylindroma type.

During the patient's three visits to the clinic, from 1939 to 1941, it was apparent that the disease had been arrested locally. On July 9, 1940, an enlarged right cervical lymph node was removed. This proved to be inflammatory. The patient's last admission was on March 9, 1942. She sought attention because of several small lumps which had recently appeared in the right side of the neck. These nodules had been somewhat tender. Examination disclosed the presence of two enlarged firm nodules in the right upper cervical region. There was no evidence of local recurrence of the malignant process.

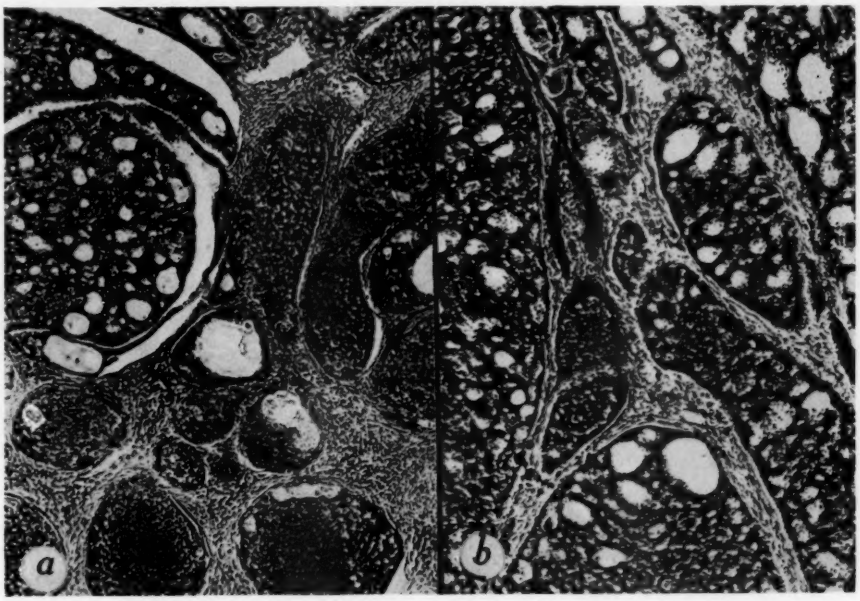

Fig. 2.—*a*, Adenocarcinoma, grade 2, cylindroma type; the primary lesion shows pronounced cellularity with a veritable honeycombing of the cylinders which vary considerably in size (hematoxylin and eosin ×60); *b*, the metastatic lesion presents a picture almost identical to that of the primary neoplasm; some of the "acini" are filled with mucus; in others the spaces appear empty (hematoxylin and eosin ×60).

At operation on March 10, 1942, these nodes were removed in a block dissection involving the right cervical chain of nodes. One of the enlarged nodules proved to be an inflammatory lymph node. The other was diffusely invaded by a metastatic grade 2 adenocarcinoma of the cylindroma type.

Pathologic Aspects.—Material for study consisted of tissue removed from the ear, from the preauricular and postauricular regions, and from the mastoid process (this last tissue had been removed prior to 1940). Available also was the metastatic nodule from the cervical region, removed on March 10, 1942. These specimens all had been preserved in formalin and were recut and restudied from blocks of tissue treated by the fixed frozen-section technique and stained routinely with hematoxylin and eosin. Stains for mucin also were employed.

Duplicating, for the most part, the picture described in connection with Case 1, certain variations were noted which merit special attention. Sections from the primary and the recurrent nodules appeared to be extremely cellular. Although in some areas the cylinders were small, in other zones they appeared very large and, indeed in some fields, a disposition in anastomosing sheets was apparent (Fig. 2*a*).

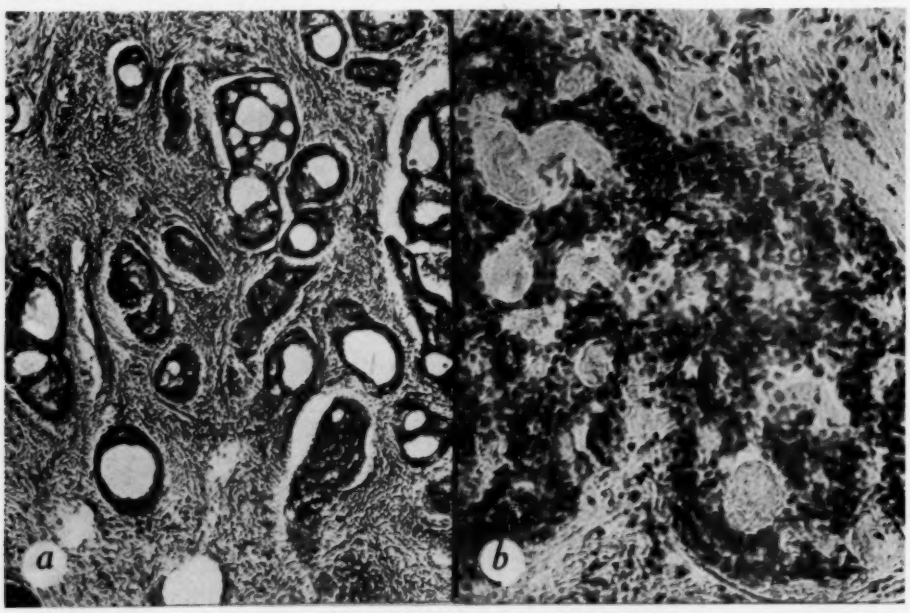

Fig. 3.—*a*, Section taken from the tissue removed for the second recurrence; thrombi of neoplastic cells are seen filling the lymphatic spaces (hematoxylin and eosin ×60); *b*, cores of the cylinders undergoing a process of hyalinization (hematoxylin and eosin ×200).

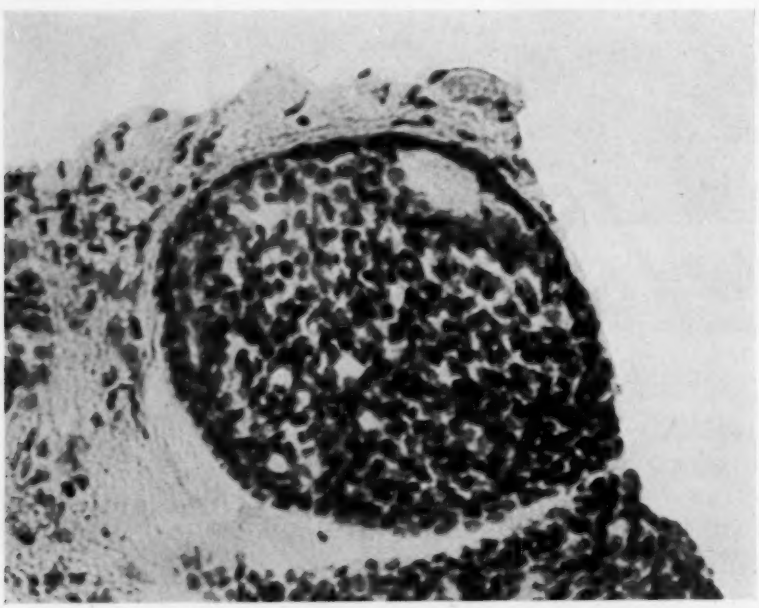

Fig. 4.—Adenocarcinoma, grade 2, cylindroma type, illustrating the cellularity of the neoplasm. The nuclei at the periphery of the cylinder appear in palisade (hematoxylin and eosin ×300).

Central "coring out" of the cylinders was extremely prominent, with a veritable honeycombing of entire fields. These "alveoli" varied considerably in size. Many of the cystic cores were empty; others were filled with a mucoid substance (Fig. 2*b*), and still others appeared to be undergoing a process of hyalinization. Under the high-power objective the general cytologic features of the cells appeared to be similar to those described for Case 1. However, in view of the greater variation in the size and shape of the cells and the finding of more than occasional mitoses, a diagnosis of grade 2 (low) adenocarcinoma, cylindroma type, seemed to fit the lesion best. No nerves were found in the sections, but thrombi of neoplastic cells were seen to have infiltrated all available lymphatic spaces (Fig. 3*a*). Special features of the metastatic nodule from the cervical region were a more pronounced tendency toward hyalinization (Fig. 3*b*) affecting both the "acini" and the stroma, and a degree of "palisading" (Fig. 4) not observed in the primary lesion. This palisading was most prominent at the peripheries of islands of tumor cells.

COMMENT

Adenocarcinoma of the cylindroma type is most frequently encountered in the parotid gland, where, according to Stein and Geschickter, the incidence is 17.4 per cent of the tumors arising therein. The submaxillary gland follows next in order, with approximately the same relative incidence of "cylindromas," but with a much smaller total number of neoplasms arising in this location. It is well known, however, that "cylindromas" can arise in connection with the lips, gums, tongue, floor and roof of the mouth, pharynx, larynx, and even the lacrimal gland. Briefly, they can occur wherever mucous glands are found about the head and neck.[1] The aforementioned locations are, in the same order of frequency, the favorable locations for the so-called mixed tumors. These characteristics, together with the fact that adenocarcinoma of the mixed tumor type is five to ten times more commonly encountered than adenocarcinoma of the cylindroma type, have combined to mask the distinction between these two forms of malignancy. The occasional discovery of neoplasms having features of both types has merely added to the difficulty. It has been our experience, however, that whenever a "mixed tumor" has exhibited cylindromatous areas microscopically, the prognosis has appeared to be almost as serious as it would be if the neoplasm existed as a pure "cylindroma."

Is the term "cylindroma" used ill advisedly in connection with neoplasms of this unusual type? Probably not, if the prefix *adeno*carcinoma is used to indicate an origin from glandular epithelium, so that confusion of the tumors with cylindromas of the skin is thereby avoided. This last mentioned type of neoplasm is a basal-cell epithelioma which is usually associated with a good prognosis.

The relatively long clinical history in each of these two cases of "cylindroma" is in keeping with our findings in connection with similar lesions of the submaxillary gland. It adds further to the difficulty of preoperative separation of the tumor from some of the more rapidly growing examples of mixed tumor. The persistent pain suffered by both patients recalls the frequency of pain (70 per cent) noted in our series

of submaxillary tumors. Finally, it is noteworthy that in both patients concerned in this report metastasis developed while the primary lesion seemingly was being controlled by local treatment. This observation emphasizes further not only the importance of the early recognition of "cylindromas" but also the necessity for a reserved, if not a guardedly bad, prognosis.

SUMMARY

Two examples of metastasizing adenocarcinomas of cylindroma type are recorded. These tumors can arise from many situations about the head and neck. They are sometimes confused with the more commonly occurring mixed tumors, but should be carefully delineated from the aforementioned group because "cylindromas" demand early treatment of a vigorously radical nature.

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PROBLEMS IN THE SURGICAL MANAGEMENT OF DIABETIC GANGRENE

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THE surgical treatment of diabetic gangrene has presented a problem of increasing interest since the discovery and general use of insulin. Twenty years ago coma was the major complication and cause of death in diabetes mellitus. Relatively few patients with a severe form of the disease lived past midlife, and surgical deaths were proportionately infrequent. Joslin[8] found that 51 per cent of a series of 1,147 diabetic deaths prior to 1922 resulted from coma, while only 9.8 per cent could be attributed to surgical complications. At the present time coma is responsible for less than 5 per cent of the diabetic deaths. These patients now survive until the sixth or seventh decades, when heart disease or infection and gangrene of the lower extremities is the principal cause of death.

The purpose of this paper is to report our experience in the surgical management of diabetic gangrene at the University of Nebraska during the ten-year period from 1932 to 1942. The patients were all seen in the University Hospital, a teaching institution with 250 beds which accepts only charity patients from the entire state. This analysis covers a decade marked by prolonged drouth and repeated crop failures in this area. The majority of patients came to us from small rural communities, farms, and ranches. Many were first seen by their local physician when infection or gangrene of an extremity was well established and were immediately referred to the hospital for emergency surgery. It is obvious that problems encountered with such a group of patients will differ from those in private practice or even on a charity service in one of our large urban centers. Regular care or attendance at a medical clinic with supervision of the diet, insulin, and care of the extremities has not been the rule in those who were known to have diabetes. These factors must be kept in mind in considering the analysis of our results in the treatment of diabetic extremities with infection and gangrene.

From 1932 to 1942 admissions of patients with diabetes mellitus to the University Hospital were 802. Of these admissions, fifty-three diabetic patients with infection or gangrene of the lower extremities have been seen on the surgical service, an incidence of 6.6 per cent. John[7]

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reported that the incidence of gangrene in diabetic patients varies from 2.4 to 18 per cent in the reported series; the average in thirteen large clinics is 5.2 per cent.

TABLE I

SERIES OF FIFTY-THREE PATIENTS (1932-1942)

Males, 31 cases	Youngest	44 yr.
Females, 22 cases	Oldest	79 yr.
Average age:		
First five-year group (25 cases)		60 yr.
Second five-year group (28 cases)		61.5 yr.
Males		61 yr.
Females		60 yr.

The average age of these fifty-three patients was 61 years (Table I); the youngest was 44 years and the oldest, 79 years. Joslin[9] has shown, from figures of the Metropolitan Life Insurance Company, that since 1926 the average age of the diabetic patient at death has been increased from 44 to 61 years and that the average duration of the disease is from 4.8 to 9 years. Eliason[5] reported that the average age of patients with diabetic gangrene increased seven years between the years 1926 and 1933. In McKittrick's[14] recent review of 1,036 cases of diabetic gangrene, the average age was 65 years. McKittrick and Root[11] had previously found that in 60 per cent of their patients, diabetes developed after the age of 40 years and in only 25 per cent, between the ages of 25 and 40 years. The surgeon may therefore expect the diabetic patient with gangrene of an extremity to appear during the sixth decade of life.

In our group 32 per cent were considered to have mild diabetes on admission, 59 per cent, moderate to severe, and only 9 per cent, severe. This classification is only relative since the true metabolic status of the diabetic patient can only be evaluated when all infection is controlled. The fact remains, however, that the majority of patients in whom diabetic gangrene develops are not severe diabetics when their infection is eradicated and their carbohydrate metabolism stabilized.

One of the striking facts in this small series was the presence of definite gangrene in fifteen patients, or 28 per cent, before glycosuria was discovered (Table II). Twelve patients were admitted to the hos-

TABLE II

KNOWN DURATION OF DIABETES IN SERIES OF FIFTY-THREE PATIENTS

TIME	CASES	PERCENTAGE
Unknown on admission	12	23
1 month to 1 yr.	5	9
1 to 2 yr.	4	8
2 to 5 yr.	11	21
5 to 10 yr.	11	21
Over 10 yr.	10	18

Fifteen patients, or 28 per cent, had gangrene before glycosuria was discovered.

pital before a diagnosis of diabetes was made, and twenty-one patients, or 40 per cent, had either not known they had diabetes when hospitalized or gave a history of glycosuria for less than two years. Eliason[5] found that 50 per cent of 175 patients with established diabetic gangrene admitted to the Philadelphia General Hospital were unaware that they had glycosuria.

Joslin[9] has aptly said that the surest way to produce gangrene in the diabetic patient is to keep him alive and provide inadequate treatment. This statement is amply supported by the infrequent occurrence of diabetic gangrene in patients under good medical supervision and the much higher incidence and mortality among the indigent. An example is the experience of Standard, Brandaleone, and Ralli[20] with diabetic gangrene in two series of patients. Prior to the onset of gangrene, one group had received adequate diabetic care, the other series none. In the latter series mortality from gangrene was twice as high and three times more frequent following major amputations as in the first group of previously treated patients.

The type of medical therapy received by our group of fifty-three patients prior to their admission with gangrene is listed in Table III.

TABLE III

PREVIOUS TREATMENT FOR DIABETES IN SERIES OF FIFTY-THREE PATIENTS

TREATMENT	CASES	PERCENTAGE
None	21	39
Poor	11	21
Fair	17	32
Good	4	8

Of twenty-one patients untreated for their glycosuria, fifteen were admitted without knowledge that they had diabetes. A total of 60 per cent of patients known to have diabetes had received entirely inadequate treatment, while only 8 per cent had been under good medical management. Responsibility for this poor record in the medical control of these patients is difficult to assign. Economic conditions and distance from competent medical supervision were undoubtedly important factors. In addition, the ignorance and indifference of these individuals remain obstacles to be overcome. In those who had had previous hospitalization and instruction covering diet, use of insulin, and care of the extremities, this advice was often forgotten or ignored as soon as symptoms were relieved.

Education undoubtedly can and will help reduce the incidence of infection and gangrene in diabetic patients. The increasing popularity of periodic health examinations will bring to light many cases of mild diabetes which we may expect to develop during the fifth, sixth, and seventh decades. Simplified diets and the use of protamine insulin

are making adequate control easier for the diabetic patient of limited intelligence. Greater effort must be made to impress all diabetic patients with the importance of proper care of the feet.

In Table IV the known precipitating factors preceding the onset of gangrene in our series of patients are listed. Burns from hot water bottles, blisters from tight shoes, and the injudicious paring of corns were responsible, in the order named.

TABLE IV

PRECIPITATING FACTORS PRECEDING ONSET OF GANGRENE

FACTORS	CASES	PERCENTAGE
Burns (hot water bottle)	8	14
Blisters (tight shoes)	5	9
Frostbite	2	4
Paring corns	4	8
Trauma	2	4
Unknown	32	61

Brandaleone[1] and his associates have emphasized the value of prophylactic foot care in patients with diabetes. They found in their series that special instruction in the care of the feet reduced the number of pedal infections requiring hospital admission from 10 to 4.6 per cent and the number of amputations, from 32.4 to 25.9 per cent.

Extensive wet gangrene of the toes and foot, often extending into the leg, was the most common type of lesion encountered (Table V).

TABLE V

EXTENT OF PATHOLOGY ON ADMISSION IN SERIES OF FIFTY-THREE PATIENTS

PATHOLOGY	CASES	PERCENTAGE
Penetrating ulcers of feet	9	17
Dry gangrene (limited to toes)	6	11
Wet gangrene (toes—distal foot)	6	11
Extensive wet gangrene (foot)	32	61
Unilateral involvement	34	62
Bilateral involvement	19	38

These patients with toxemia, sepsis, acidosis, and uncontrollable diabetes and with the constant hazard of gas bacillus infection present a very grave surgical emergency. Those individuals with dry gangrene, infected penetrating ulcers of the feet, or moist gangrene limited to one or two toes were not acutely ill, and their treatment did not demand the same heroic measures. It is characteristic that nineteen patients, or 38 per cent of the group, had bilateral involvement of the lower extremities when first seen.

The relationship between arteriosclerosis and diabetes is now well appreciated. Experience has shown that the arteriosclerotic process continues to advance in spite of therapy, with the result that the diabetic patient's vessels are usually ten years older than the patient. Olmsted[17] has observed that pulsations in the lower extremities of

these patients tend to disappear ten to twenty years earlier than in nondiabetic individuals. Lisa, Magiday, and Hait[10] recently reported a study of the peripheral vessels in amputated gangrenous limbs of 106 patients. Of these, approximately one-half (fifty-five) were diabetic patients averaging 65 years of age, while the fifty-one with arteriosclerotic gangrene had an average of 68 years of age. In the vessels of the two groups of patients no characteristic pathologic differences could be distinguished.

Calcification of the peripheral vessels was demonstrated by x-ray by Morrison and Bogan[16] in 53 per cent of 324 consecutive diabetic patients and was demonstrable in 91 per cent of those who were known to have diabetes for a ten-year period. X-ray studies of the lower extremities of forty-three of our patients (Table VI) showed visible

TABLE VI

X-RAY FINDINGS IN INVOLVED LIMBS IN SERIES OF FORTY-THREE PATIENTS

X-RAY FINDINGS	CASES	PERCENTAGE
No visible calcification	8	19
Moderate calcification	10	23
Marked calcification	16	37
Osteomyelitis, calcification	6	14
Gas in soft tissues	3	7

Ten patients not examined by x-ray.

calcification of the peripheral vessels in 74 per cent, with marked calcification in 37 per cent. Although a peripheral vessel demonstrating visible calcification cannot be assumed to be incapable of carrying blood, its ability to demonstrate palpable pulsations is important from the standpoint of prognosis and treatment. However, it is quite unusual to find either a pulsating dorsalis pedis or posterior tibial artery in an individual with marked calcification of the peripheral vessels. Gas in the soft tissues of the feet was noted by x-ray in three cases. This finding does not always indicate the presence of anaerobic gas-forming organisms since the colon group are capable of producing a similar picture. In two patients a diagnosis of gas bacillus infection was established by clinical and bacteriologic study, while in the third patient anaerobic organisms could not be demonstrated.

It is extremely difficult in a general hospital to standardize the treatment of any group of patients with diabetic gangrene. The problems presented by the individual case demand the closest possible cooperation between internist and surgeon. Experience in the majority of our large teaching clinics has amply demonstrated the importance of management of these patients by a small team of medical men and surgeons especially interested in these problems and equally willing to devote the required time and care. Every reported series of patients so handled has shown a striking improvement in mortality with a commendable reduction in hospital days. Our series of patients was not

thus supervised; the internist on service was responsible for the care of the diabetes and the surgeon on ward service at the time of the patient's admission was responsible for surgery. Inevitably this system will result in a higher mortality because of split responsibility, ultraconservatism of either internist or surgeon, and lack of the perfect teamwork essential in the management of these complex problems.

In the surgical treatment of patients with diabetic gangrene, the selection of the anesthetic agent is extremely important. The ideal anesthetic has a wide margin of safety, permits satisfactory performance of the proposed procedure, does not lower local tissue resistance, and interferes as little as possible with the patient's metabolism. Pentothal sodium has been our choice in minor surgical procedures, including amputation of toes, débridement, incision, and drainage. Low selective spinal anesthesia, using 50 mg. of novocain, has been very satisfactory for all major amputations. When an inhalation anesthetic was necessary, cyclopropane was preferred to nitrous oxide or nitrous oxide and ether. We have had no experience with anesthesia by reduced temperatures as recently advocated by Crossman and associates.[2]

For all procedures of election the patient is given his regular breakfast with necessary insulin at 7 A.M. After a period of three hours, surgery is carried out under pentothal or spinal anesthesia with little risk of nausea or vomiting. Two hours after operation orange juice is permitted by mouth and by evening the regular diabetic diet. Those admitted as surgical emergencies, requiring prompt débridement or open amputation, are given intravenous glucose covered with insulin to correct acidosis. Following operation they are given orange juice with necessary insulin at four-hour intervals; a diabetic diet is prescribed by the attending internist as soon as it can be tolerated.

TABLE VII

TREATMENT IN SERIES OF FIFTY-THREE PATIENTS

TREATMENT	CASES	PER CENT	MORTALITY	
			CASES	PER CENT
Conservative therapy	17	32	2	12
Conservative surgery				
Incision and drainage	3	7	0	0
Toe amputation	7	13	0	0
Primary major amputation	19	35	7	37
Primary conservative surgery with subsequent major amputation	7	13	2	28
Major amputation requiring reamputation	2	4	1	50

There was a hospital mortality of 12 patients in series of 53, or 22.6 per cent.
There was an operative mortality of 10 patients in series of 36, or 27.7 per cent.

An outline of surgical treatment is given in Table VII. Conservative therapy with or without minor surgical procedures was used in twenty-seven patients, or 52 per cent of the series. In this group only two deaths occurred, both in patients admitted in extremis. It would be

ideal if all patients with infection or gangrene might be admitted sufficiently early to make conservative measures more frequently feasible, with resultant saving of limbs. Primary major amputation in nineteen patients resulted in seven deaths, a mortality rate of 37 per cent. In two patients major amputation required reamputation, with one death; and seven patients with primary conservative surgery were followed by subsequent major amputation, with two deaths. In this whole series of fifty-three patients, twelve died, a mortality of 22.6 per cent. Of the thirty-six patients operated upon, ten died, a surgical mortality of 27.7 per cent.

In an analysis of the mortality rate for major amputations in diabetic patients reported by sixteen surgeons, John[7] found a variation of from 5 to 65 per cent, depending upon the hospital and the type of patient. Williams and O'Kane[21] report that institution of a diabetic service reduced mortality from 85 to 36 per cent in a four-year period. Zierold's[22] mortality in major amputations dropped from 50 to 10 per cent in one year's time after institution of a two-stage procedure in the care of extensively infected patients. Pearse and Ziegler[18] record a similar decrease in mortality from 45 to 12 per cent. McKittrick[14] recently reported a commendable mortality rate of only 11.5 per cent in a series of 407 patients with diabetic gangrene subjected to a closed supracondylar amputation. This procedure, in the presence of extensive wet gangrene or infection, followed a previous open guillotine amputation below the knee.

The highest mortality in our group occurred in the nineteen cases of primary thigh amputation, a result to be anticipated in patients with extensive spreading infection, wet gangrene, and marked sepsis. Of this group, four succumbed to gas gangrene involving on admission the entire leg in two cases and arising in the amputation stump in the other two (Table VIII). Bilateral gangrene accounted for one death and sepsis and pneumonia for the remaining two fatalities.

TABLE VIII

ANALYSIS OF CAUSE OF DEATH IN SERIES OF TWELVE PATIENTS

CAUSE OF DEATH	CASES	PERCENTAGE
Sepsis, arteriosclerosis, pneumonia	7	58
Gas bacillus infection		
Arising in amputation stump	2	17
Extensive involvement of limb	2	17
Toxemia, bilateral gangrene	1	8

For the last two years we have increasingly used a two-stage procedure in these desperately ill patients with wet gangrene, plantar space abscess, or spreading infection limited to the foot. Correction of ketosis is followed by extensive débridement of all infected and gangrenous tissue or wide incision, as suggested by Zierold.[22] Definite clinical improvement is usual, with return of normal temperature and

rapid relief from sepsis. After three days of normal temperature, a high amputation at the site of election is carried out in a patient whose general condition is greatly improved. McKittrick,[13] Pearse and Ziegler,[18] and also Gallie[6] advocate the employment of such a two-stage procedure but favor a guillotine amputation through the leg followed in a suitable period by a closed amputation at the supracondylar level. Our patients with infection and gangrene extending above the ankle have been treated by an open circular amputation in the midthigh with subsequent secondary closure.[15]

TABLE IX

TYPES OF MAJOR AMPUTATIONS EMPLOYED

AMPUTATIONS EMPLOYED	CASES	PERCENTAGE
Circular midthigh drained	17	61
Circular midthigh not drained	4	14
Callander, no drain	4	14
Flap amputation below knee	3	11

There were twenty-eight major amputations in twenty-six patients.

A midthigh amputation with short anterior and posterior flaps was the most common procedure employed in this series of patients (Table IX). The type of amputation described by Callander was used four times; three patients had flap amputation below the knee, but this type of procedure has not been employed recently, and, in general, its use is not advisable in diabetic patients.[3, 4, 11] Anatomically the Callander amputation gives an excellent stump, but the considerably longer operative time required is often a distinct disadvantage. Our preference for the midthigh level has been dictated by the extent of pathology present and by the fact that such patients very rarely improve sufficiently to wear an artificial limb. The closed supracondylar amputation advocated by McKittrick[13, 14] and Samuels[19] is commendable in reducing time required for wound healing and the excellent stump which results. However, this type of closed procedure demands a clean operative field, meticulous technique, and previous control of any spreading infection in the adjacent leg.

Our experience with wound healing in these diabetic stumps confirms the dictum of Eliason that "clean wounds in diabetes do not heal as kindly as in nondiabetics."[5] He has reported that some form of infection with severe diffuse suppuration developed in 42 per cent of the amputation stumps in a large series of patients. In our series of 28 major amputations, definite wound infection developed in sixteen patients, or 57 per cent (Table X). Drainage for forty-eight hours was used in twenty patients, in twelve of which (60 per cent) frank wound infection developed. The wounds failed to heal by primary union or became infected in four of the remaining eight patients who had closed amputations. The controversy over use of drains after major amputations for diabetic gangrene is familiar to all interested in this type of

TABLE X

WOUND HEALING IN SERIES OF TWENTY-EIGHT MAJOR AMPUTATIONS

	CASES	CLEAN WOUNDS		INFECTED WOUNDS	
		CASES	PER CENT	CASES	PER CENT
Circular midthigh drained	17	6	35	11	65
Circular midthigh not drained	4	1	25	3	75
Callander, no drain	4	3	75	1	25
Flap amputation below knee	3	2	66	1	33

surgery. In the majority of our series drains were deemed advisable because of the extensive adjacent infectious process, the frequency of gas infection, and the needed exit for serum. The trend of the past few years has definitely been toward nondrainage. Admittedly a drain may permit entrance of organisms into a clean wound and delay healing in tissue of low vitality, but if these amputation stumps are closed without drainage, any adjacent infection in the leg must be stabilized, hemostasis must be meticulous, and the possibility of a gas infection in the stump constantly kept in mind. The two-stage procedure in cases of extensive spreading infection, together with local use of sulfonamides, will undoubtedly reduce the number requiring drainage and will increase the number of clean wounds.

Diabetic gangrene is an extremely expensive disease, as proved by hospital records. Since the majority of these patients are aged and without funds, their care becomes the responsibility of charity or the taxpayer. The average number of hospital days for our entire series of 53 patients was 47.4 days; of those who survived, fifty-two days (Table XI). These figures agree with those of Eliason,[5] who reported

TABLE XI

DAYS OF HOSPITALIZATION IN SERIES OF FIFTY-THREE PATIENTS

	DAYS
Average for entire group	47.4
Average for fatal cases	29
Average for nonfatal cases	52
Average for fatal operative cases before surgery	13.3
Average length life (fatal cases after surgery)	3

an average of 36.5 hospital days for his entire group of 170 patients and an average of 62.2 days for those who recovered.

Further analysis of our series discloses that those who succumbed following operation were in the hospital for an average of 13.3 days before surgery was undertaken. In certain cases it is thus apparent that entirely too long a period of conservative medical treatment intervened before surgical consultation was requested. The diabetic patient with wet gangrene or spreading infection will not and cannot respond to medical treatment until the infection is overcome by surgical means. Conservatism on the part of the medical attendant can be quite as disastrous as the same tendency in the consultant surgeon. The degree

of success attained in the management of patients with diabetic gangrene depends upon the close cooperation of a competent internist and surgeon, each accepting full responsibility for his part of the problem from the time of the patient's admission to the hospital.

Follow-up studies on any series of patients with diabetic gangrene are extremely discouraging. McKittrick and Pratt[12] found that only 33 per cent of 188 patients were alive two years after operation, and of these 34 per cent had had bilateral amputation. Eliason[5] reported that 55 per cent of his series of 175 patients were dead within one year after operation. Our follow-up on this series of patients, while incomplete, suggests similar results with approximately 50 per cent being dead within one year after their dismissal from the hospital. Few patients have recovered sufficiently to return to their former work or pursue any gainful occupation.

CONCLUSIONS

1. A group of fifty-three patients with diabetic gangrene occurring in a series of 802 patients admitted with diabetes is reviewed.

2. Adequate medical treatment of the diabetic patient and meticulous care of the extremities are the most important factors in reducing the incidence of diabetic gangrene.

3. Improved surgical results follow the more general appreciation of the underlying surgical principles governing the care of diabetic gangrene.

4. Close cooperation of an internist and surgeon familiar with these problems is essential if these critically ill patients are to receive adequate treatment.

5. Diabetic gangrene is an extremely expensive disease. The period of hospitalization is usually protracted, and few patients improve sufficiently to return to any gainful occupation.

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STUDIES IN BACTERIOPHAGE

VII. The Behavior of Staphylococcus Bacteriophage in Human Serum and Blood

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INTRODUCTION

MANY papers on staphylococcus bacteriophage have shown that the lytic activity is affected by such body fluids as blood, serum, and pus. Most of these studies are concerned with the power of serum to inhibit bacteriophage lysis. A review of this work has been reported in a previous communication.[1] We agree that nearly all normal human sera undiluted or in a 50 per cent dilution prevent bacteriophage lysis of bacteria in liquid medium in vitro. There is some effect, permanent or passing, with dilutions of 1 in 10 and 1 in 20, while higher dilutions are generally ineffective.[2-9] Repeated subcutaneous, intramuscular, and intravenous injections of bacteriophage into human beings or experimental animals may increase the phage-inhibiting power of their serum up to a level of complete phage inactivation. This antiphage is either very much more potent than, or of an entirely different nature from, that found in normal individuals.

A few authors have shown that defibrinated or citrated blood also may inhibit staphylococcus-bacteriophage lysis.[5, 6]

On the basis of these findings, investigators have been led to believe that bacteriophage is inactivated within the body. However, observations on bacteriophage action in vivo do not fully support this idea. The recovery of bacteriophage from the body is difficult to explain on the basis of complete phage destruction by the blood or other body tissues. Potent staphylococcus phage has frequently been found in the exudate from a human lesion caused by staphylococci. We have isolated spontaneous staphylococcus phages from about 5 per cent of the cases of acute staphylococcus infections (furuncles and carbuncles) and whenever we have recovered bacteriophage from a lesion it has always been accompanied by a susceptible organism. According to Albee[10] the percentage of phage recovery may be much higher in chronic infections (osteomyelitis) and yet the lesions are usually filled with pus and tissue fluids. Two of our most potent polyvalent staphylococcus phages were isolated from the blood stream of patients suffering from staphylococcus septicemia, despite the fact that the blood of one such patient inhibited lysis by the recovered bacteriophage in liquid medium up to a dilution of 1 in 40.

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It is true that bacteriophage injected intravenously either into normal patients or animals can only rarely be recovered from the blood after 24 hours. This is due in part to the excretion of phage in the urine, from which it can be recovered readily. However, the delay in the growth and the character of the colonies on blood agar plates when transplanted from broth blood cultures in cases of staphylococcus septicemia suggest the continued activity in the blood, 24 to 48 hours after intravenous injection. Furthermore, we have found that bacteriophage injected locally into furuncles and carbuncles may, in some cases, persist for a week and yet the serum of one such patient inhibited phage lysis in high dilutions in liquid as well as on solid media.[1]

It seemed to us to be worth-while to investigate these apparent inconsistencies. Therefore the studies presented herewith were planned.

EXPERIMENTAL TECHNIQUE

The blood and serum of fifteen individuals were repeatedly examined. Four of these were suffering from chronic furunculosis of several months' or years' duration. Ten, classified as normal, were completely well but two had had occasional staphylococcus infections in the past. One individual had received previously twelve subcutaneous injections of phage in an attempt to prevent recurrent boils, and had built up a strong phage-inhibiting factor in the serum (antiphage).

In the series to be presented, we studied 50, 66, and 100 per cent serum as well as undiluted, defibrinated, and heparinized blood. The serum dilutions represent the limits of the actual concentration of plasma in the blood.[11] Heparinized blood contained 750 units of heparin per cubic centimeter.[12] Citrated blood was not included in the experiments, previous work having shown that sodium citrate itself has a deleterious effect on bacteriophage.

Most of the experiments were set up either with 0.9 c.c. or 1.8 c.c. amounts of blood or serum undiluted or diluted in saline solution, and 0.1 c.c. of undiluted or diluted bacteriophage. A 5- to 6-hour-old *Staphylococcus aureus* culture in Savita, a yeast extract broth low in protein, diluted down to the fifth decimal dilution, was used in most of the experiments, in 0.1 c.c. amounts yielding about 100 to 500 colonies on the plate.

The titer of the phage was determined by counting plaques when the 10^{-5} and 10^{-6} dilutions were inoculated with approximately 250 million bacteria per cubic centimeter and 0.01 c.c. of each of these phage-bacteria mixtures was plated on a quadrant of a 1 per cent agar plate, which was then incubated overnight. An estimation of the lytic ability of the undiluted phage was made by inoculating a quadrant of an agar plate, first with 0.01 c.c. of a saline suspension of bacteria containing 250 million bacteria per cubic centimeter and then with 0.01 c.c. of the phage.

Staphylococcus-phage stock mixture S_1 and bacterial strain D (a staphylococcus isolated from a case of septicemia) were used for the

most part. Many of the experiments were repeated with a pure strain of bacteriophage D'A and staphylococcus strain McA, also isolated from a case of septicemia.

All experiments were carried on for 1 week at 37° C. and at room temperature for the remainder of the experiment. Titrations were made at varying intervals, sometimes as early as 3 to 6 hours, and repeated after 24 and 96 hours, in some experiments also after 48 and 72 hours, always at 7 days, and often at longer intervals up to 4 weeks. Owing to the long duration of these experiments and the small quantities of blood which we were forced to use, it became necessary, usually at the time of the 7-day titration, to dilute the blood and the corresponding savita control with 1.0 c.c. of savita broth to compensate for evaporation.

RESULTS

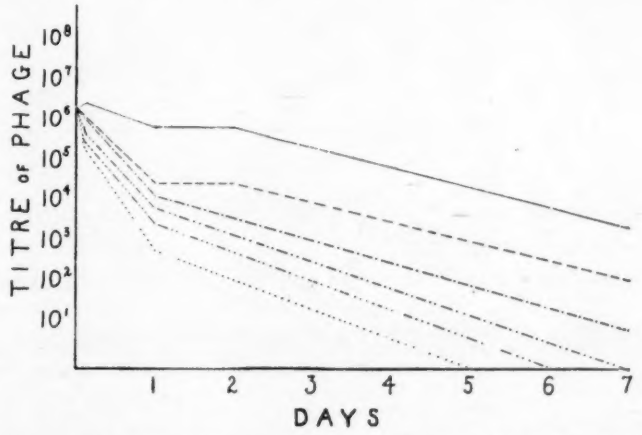
The Behavior of Bacteriophage S_1 After Contact With 50 Per Cent, 66 Per cent, and Undiluted Human Serum and Heparinized and Defibrinated Blood in the Absence of Susceptible Bacteria.—These experiments were conducted with two sera (B and C) from "normal" persons who had had an occasional staphylococcus infection and two sera (A and D) from patients suffering with chronic furunculosis. The effects on phage of the undiluted sera and the 50 and 66 per cent dilutions in saline were studied by titration of the bacteriophage on solid medium after contact for 3 hours, 24 hours, 96 hours, and 7 days with 0.1 c.c. of undiluted phage S, at 37° C.

At no time throughout the experiment did we find any significant difference between the sera from the normal persons and the sera from the chronically ill patients. All dilutions showed a progressive inhibiting effect upon phage, which was most marked within the first 24 hours and brought about complete or nearly complete destruction of all phage at the end of a 7-day period. The degree of inhibition depended directly upon the concentration of the serum.

Parallel experiments were then carried out with whole blood. Heparinized and defibrinated bloods O and M from "normal" individuals were used. Our results showed a very close similarity in the phage inhibitory effect of these two bloods. The effect was slightly below that of 66 per cent serum. Heparinized blood produced a slightly greater destruction than did defibrinated blood. The titer of phage in savita broth also fell during the 7-day period, the chief difference being the more rapid loss of titer of phage in contact with serum or blood in the first 24 hours. Composite curves are shown in Fig. 1; individual tests were practically identical.

The Behavior of Bacteriophage in Savita Broth, in 66 Per Cent Serum, and in Heparinized and Defibrinated Blood in the Presence of Susceptible Bacteria.—Whole defibrinated and heparinized blood and 66 per cent serum from patients O and M were studied in the presence and in the absence of bacteria. Fig. 2 shows the results obtained with

blood M. Neither 66 per cent serum nor whole blood produced any inhibition of bacteriophage in the presence of bacteria after 24 hours. There was actually an increase in the titer during this period. Between 24 and 96 hours the titer of phage remained the same, and then after 7 days a further increase occurred in the blood. This was slightly more pronounced in the presence of defibrinated blood than in heparinized blood or serum. In 66 per cent serum a very slight fall was observed. The results with blood O were similar except for the fact that in 24 hours there was a slight drop in titer. This increased after 96 hours of incubation, and increased still more after 7 days. In the savita control there was a fall in the titer of phage both with and without bacteria, although with bacteria there was an initial rise. There was the usual degree of phage inhibition of all three substances in the absence of bacteria.



_ Titer of phage control in savita broth
_ _ Titer of phage in 50 per cent serum
_·_ Titer of phage in whole defibrinated blood
_···_ Titer of phage in whole heparinized blood
_····_ Titer of phage in 66 per cent serum
····· Titer of phage in undiluted serum

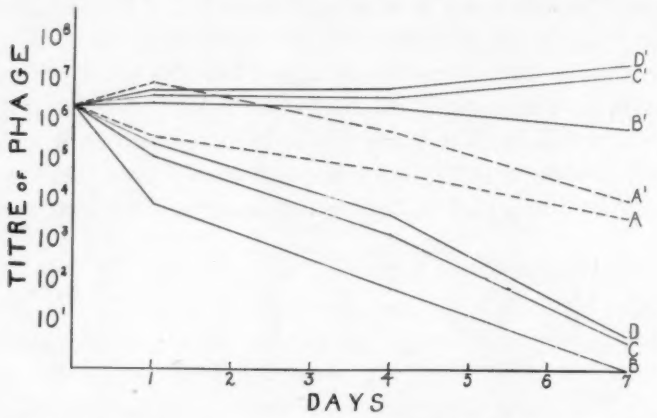
Fig. 1.—Effect of undiluted, 66 per cent, 50 per cent serum, whole defibrinated and heparinized blood on Staphylococcus bacteriophage in the absence of bacteria.

To study this phenomenon in greater detail we tested nine additional bloods. Of these, six were taken from normal individuals, two (S and K) from patients suffering with chronic furunculosis, and one (J) from an individual who had received twelve subcutaneous injections of phage in an effort to prevent recurrent furunculosis.

Undiluted Phage.—Fig. 3 shows the activity of undiluted phage S_1 containing approximately 5×10^8 corpuscles per cubic centimeter in seven specimens of blood in the presence of bacteria. In 3 to 6 hours in each of the specimens there occurred a drop in titer. Then a sharp upward trend began, usually reaching the maximum titer in 24 to 48 hours. In 7 days, upon the addition of 1 c.c. of savita broth, to compensate for evaporation and the amounts taken for titration, a further increase in phage titer was observed in two of five which were so studied. In three a high level was maintained from the second to the fourth week. The savita control also showed a drop in titer during the first 3 to 6

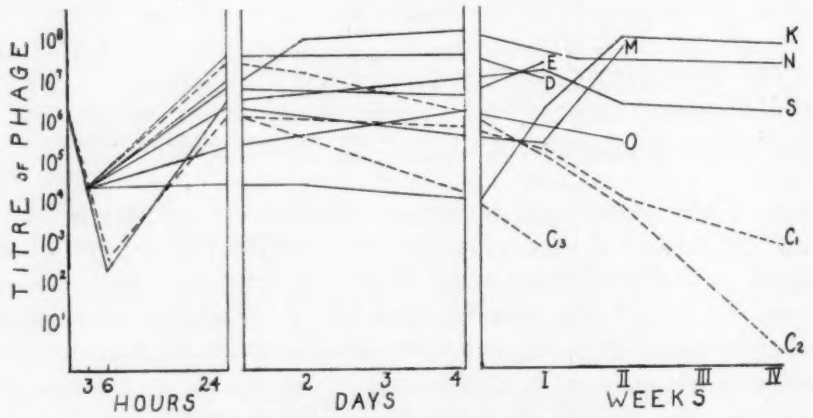
hour period and an increase in 24 hours. Upon further incubation there was a definite downward trend which continued and was slightly or in no way affected by the addition of 1 c.c. of fresh savita on the seventh day.

Phage Diluted 100 and 1000 Times.—Fig. 4 shows the activity of a 10^{-2} dilution of phage, S_1, in the presence of bacteria in nine specimens



A. Phage in savita
B. Phage in 66 per cent serum
C. Phage in heparinized blood
D. Phage in defibrinated blood
A'. Phage in savita with bacteria
B'. Phage in 66 per cent serum with bacteria
C'. Phage in heparinized blood with bacteria
D'. Phage in defibrinated blood with bacteria

Fig. 2.—The effect of 66 per cent serum M, whole defibrinated and heparinized blood M on Staphylococcus phage S_1 after 24 hours, 96 hours, and 7 days' incubation in the presence and absence of fifty susceptible organisms per cubic centimeter.



——— Titer of phage in bloods O, M, K, S, N, D, E
- - - - Titer of phage in savita control: C_1, C_2, C_3

Fig. 3.—Titer of undiluted Staphylococcus phage S_1 propagated in defibrinated bloods O, M, K, S, N, D, E in the presence of susceptible bacteria.

of blood. Four of these bloods are the same as those used with undiluted phage. From this chart we can see that in all cases there occurred an initial drop in phage titer between 3 to 6 hours.

In 24 hours a considerable amount of individual variation in phage activity in different bloods can be seen clearly. In four specimens of

blood there was a definite multiplication of bacteriophage. In one of these four bloods the phage reached the original titer, that is, it multiplied 1000 times in 24 hours. In four other bloods the titer continued to rise after 24 hours. When 1 c.c. of savita was added to the tubes on the seventh day of incubation the titer often continued to increase. In those cases which reached a high titer the bacteriophage maintained this level for at least 4 weeks, the duration of the experiment. In three bloods a gradual decrease of the phage titer occurred so that within 1 week all traces of phage had disappeared and the addition of savita on the seventh day failed to revive them.

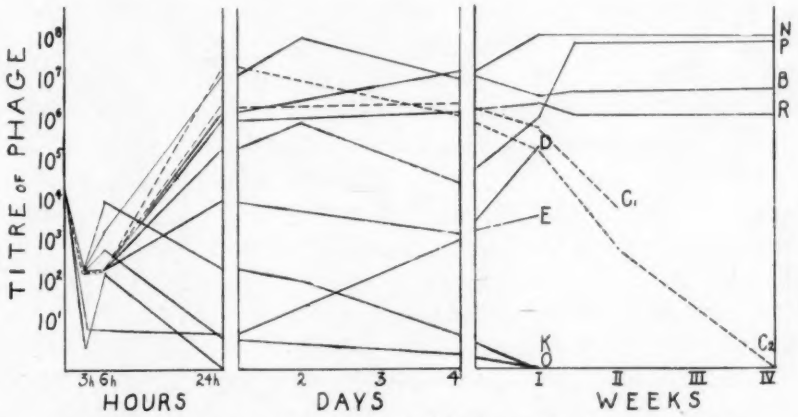


Fig. 4.—Titer of 10^{-2} dilution of Staphylococcus phage S_1 propagated in defibrinated bloods O, K, P, R, B, D, E and N in the presence of bacteria.

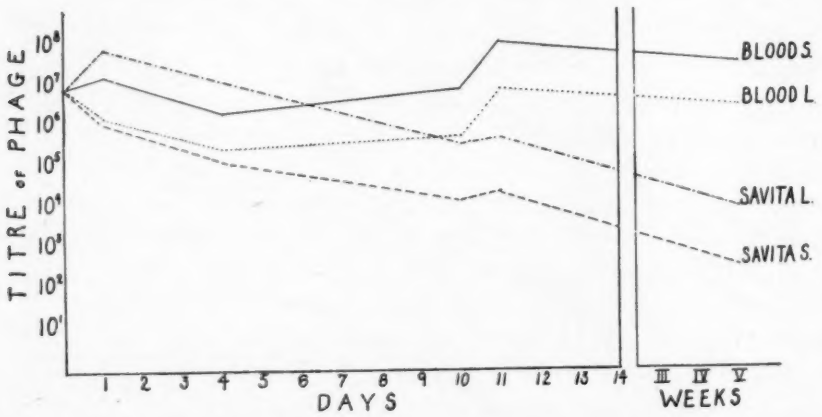
In one blood (E) the bacteriophage seems not to have multiplied at all, but it did not disappear upon incubation.

The corresponding control of 10^{-2} dilution of phage in savita reached its maximum titer within 24 hours. After this time the titer steadily decreased and phage disappeared in spite of the addition of a fresh savita inoculum on the seventh day.

Bacteriophage S_1 in a dilution of 10^{-4} was propagated at the expense of a small number of bacteria in five specimens of blood. In four of these specimens all evidence of phage disappeared in 3 to 48 hours. Only in one blood was there a definite indication of bacteriophage multiplication. The phage controls in savita behaved similarly to those in a dilution of 10^{-2}.

Effect of Undiluted Blood on Bacteriophage in the Presence of Different Amounts of Bacteria.—In this experiment a series of four tubes with 0.9 c.c. of heparinized blood plus 0.1 c.c. of phage were inoculated with 100, with 10,000, with 1,000,000, and with 200,000,000 bacteria respectively, all being suspended in 0.1 c.c. of savita. Four tubes of savita broth plus phage suspensions were inoculated with bacteria in a similar way as controls.

Titrations were carried out at varying periods of time from 24 hours to 25 days of incubation. The blood containing 100 bacteria per cubic centimeter gave a higher count than that which contained a greater number of bacteria. On the other hand, the titer of phage propagated in savita was the highest when propagated at the expense of 200 million bacteria and lowest in the presence of an inoculum of 100 bacteria per cubic centimeter. Fig. 5 shows the titer of phage S_1 propagated in blood and savita at the expense of 100 bacteria and 200 million bacteria per cubic centimeter respectively. These experiments were repeated with the same result with other specimens of heparinized and defibrinated blood.



— Blood S. No. = 100 bacteria per c.c.
... Blood L. No. = 200 million bacteria per c.c.
- - - Savita S. No. = 100 bacteria per c.c.
-.-. Savita L. No. = 200 million bacteria per c.c.

Fig. 5.—Effect of whole blood on Staphylococcus phage in the presence of different amounts of bacteria.

DISCUSSION

Most workers in the field of bacteriophagy accept the reported observations that blood inactivates phage or prevents its lytic action and have assumed, therefore, that the clinical benefit seen following bacteriophage therapy in cases of bacterial infection cannot be due to bacterial lysis in vivo. Such an opinion is expressed by Krueger and Scribner in their recent review of the bacteriophage problem.[13] They state this rather emphatically and say that if bacteriophage is of any benefit in such cases the explanation will have to be found in one or more of the other possibilities, namely (1) increased leucocytosis and phagocytosis, (2) bacterial dissociation with avirulent progeny, (3) the stimulation of antibacterial immunity of a specific or nonspecific nature or (4) protein shock.

Our experience with bacteriophage in the treatment of staphylococcus septicemia would seem to cast doubt upon items (4) and (3) because we have propagated our phage in savita medium, which is practically protein-free, and we seldom see any reaction indicative of protein shock. Furthermore, the clinical benefit is often apparent in 24 to 48 hours

before there can be any time for the development of immunity and before any antibacterial substances can be demonstrated. With regard to bacterial dissociation the question arises whether dissociation can take place without associated bacterial lysis. This factor cannot be ruled out. Increased leucocytosis and phagocytosis may take place but this is not a striking feature of patients who recover, nor is a falling leucocytic count indicative of a bad prognosis.

The studies presented above indicate that the possibility of bacterial lysis and propagation of bacteriophages in vivo must be given further consideration. We have obtained potent spontaneous bacteriophages from the blood of patients with staphylococcus septicemia before the injection of our stock bacteriophage. We have obtained phage from the urine after intravenous injection. We have occasionally found phage in pus, which yielded no bacterial growth, 24 hours after local instillation of stock phage into local lesions. These observations in addition to the above data would seem to support the belief that phage may at times propagate and produce lysis in vivo.

There is evidence that every specimen of human blood is capable of destroying a certain number of bacteriophage corpuscles. Knowing that 0.1 c.c. of 10^{-4} dilution of phage in 0.9 c.c. of blood contains approximately five times 10^{+4} bacteriophage corpuscles we can conclude that many bloods are capable of destroying this number of phage corpuscles; some bloods seem capable of destroying an even higher number.

The clearest picture of the effect of blood on phage is obtained with the 10^{-2} dilution because it brings out the difference between the inhibiting power of different bloods. This test might be used to indicate which bloods will permit and which will prevent the multiplication of phage, and in what cases very large doses of phage are indicated therapeutically.

In contrast to this, when undiluted phage is used the number of phage corpuscles which survive are able to propagate in every specimen of blood. This suggests that provided a sufficiently large amount of potent bacteriophage is injected intravenously, there will be a certain number of corpuscles which will escape any deleterious effect of blood and will begin to multiply. The same should hold true in cases of local lesions caused by staphylococci.

In the presence of blood or serum the optimum ratio for lysis of phage corpuscles to bacterial cells may change because the blood or serum may either favor or retard the growth of the bacteria or favor or retard the lytic action of the phage.

The deterioration of bacteriophage in vitro is a phenomenon of considerable practical importance. Not until some way is found invariably to develop potent phages and to maintain the potency over a long period of time can we expect effective phages to be prepared commercially and used extensively. Researches in this direction are being carried on and will be reported in subsequent papers.

It must be constantly borne in mind that the action of bacteriophage in vitro differs from that in vivo. In the latter the blood is constantly renewed and the pH maintained and the blood stream has an exceedingly strong bactericidal action both in the blood elements and the phagocytic power of the capillary endothelium. Blood cultures suggest that the number of viable organisms is usually less than 200 per cubic centimeter. In vitro the blood is not renewed; the cells die off, the phagocytic power is gradually lost, and there is less inhibition of the growth of the organisms.

If doses of bacteriophage are given in amounts ranging from 50 to 100 c.c. a day, the dilution in the body becomes approximately 1 to 100. With viable bacteria in the blood stream ranging from 20 to 500 organisms per cubic centimeter our experiments suggest that the propagation of phage and the lysis of bacteria in vivo are well within the range of possibility. Our experiments also suggest that bacteriophage should be given in as large quantities as possible in order to favor this function. Furthermore, it should be given daily in divided doses until a favorable result is obtained as indicated by the disappearance of a positive blood culture. Further studies will have to be made in order to find out why certain bloods inhibit bacteriophage, and an effort made to prevent this inhibition. In all studies of bacteriophage, emphasis should be placed upon the potency of the phage. It should be clearly stated whether the criterion of potency is the clearing of the culture in fluid medium or the complete inhibition of bacterial growth as indicated by the absence of colonies when the cleared culture is transferred to the blood agar plate (double potency test).[10]

SUMMARY

1. All specimens of human blood brought into contact with undiluted staphylococcus phage containing an average of $5 \times 10^{+8}$ corpuscles per cubic centimeter in the absence of bacteria produced a gradual inactivation of the phage, which was most marked within the first 24 hours and after 7 to 14 days all of the phage was usually destroyed.

2. Human serum produced a similar phage-inactivating effect, the degree of inactivation depending on the concentration of serum; undiluted and 66 per cent serum possessed a higher phage-inhibiting effect than whole defibrinated or heparinized blood, and 50 per cent serum had a slightly lower effect.

3. There was no significant difference in the phage-inhibiting effect between the blood or serum of individuals suffering from chronic furunculosis and the blood or serum of normal people.

4. When staphylococcus phage suspensions containing 5×10^{8} corpuscles per cubic centimeter were incubated in whole blood in the presence of susceptible bacteria, bacteriophage was never completely inactivated by any of the bloods tested, and multiplication of phage occurred within 24 hours in most of the bloods.

5. Phages propagated in the blood at the expense of 100 bacteria per cubic centimeter reached a higher titer than did phages propagated in the blood at the expense of 200 million bacteria. This was contrary to the behavior of phage when propagated in savita.

6. When 10^{-4} dilutions of phage containing an average of 5×10^4 corpuscles per cubic centimeter were incubated in blood in the presence of susceptible bacteria, a complete inactivation of phage within 3 to 48 hours took place in most of the tested bloods.

7. Thus, the survival and lytic power of phage in blood probably depends to a considerable degree on the concentration of phage corpuscles. If this number exceeds the amount which the blood can destroy, multiplication of phage in the blood may subsequently take place.

8. The use of staphylococcus phage in dilution 10^{-2} containing an average of 5×10^6 corpuscles in blood in the presence of susceptible bacteria makes it possible to distinguish between those bloods which will and those which will not allow the multiplication of phage corpuscles.

9. On the basis of these experiments we believe that multiplication of phage takes place in blood and other body fluids in vivo provided that a sufficiently large amount of potent phage is used.

We wish to express our appreciation for the technical assistance of Miss Catherine Capraro and Miss Olga Mordvin.

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INFARCTION OF THE GALL BLADDER

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GANGRENE of the gall bladder without infection and due to infarction is uncommon. In 1929 Vest[1] reviewed eighty cases of gangrene of the gall bladder, not including the sixty cases reviewed by Baumgartner[2] of the Mayo Clinic. Vest listed the following causes of gangrene of the gall bladder: (1) infection; (2) edema of structures adjacent to the cystic vessels; (3) stones plus infection and pressure; (4) mechanical factors, including (a) torsion, (b) angulation of the cystic duct by distention, (c) glands or tumors, (d) embolism or thrombosis of the cystic ducts (no proved case) and (e) distention spasm. Mark[3] reported four cases of gall bladder infarction. In two of these there was arterial change, and in two there was venous thrombosis. Mark described five varieties of vascular disturbances and said he believed that arteriosclerosis is an etiologic factor.

As Judd and Waldron[4] have pointed out, there is no accurate guide to the diagnosis of gangrene of the gall bladder. There may be marked tenderness and rigidity in the right upper quadrant, but the symptoms may be mild.

CASE REPORT

A widow, 59 years of age, was admitted to the Evanston Hospital on March 26, 1942. For thirty-two hours she had suffered from continuous pain in the right upper quadrant. Several hours after the onset of the pain she began to have nausea and vomiting.

The past history was not significant except for the preceding six weeks, during which time she was under treatment by an osteopath for "sciatica" and multiple joint pains. Large doses of empirin compound were taken during that period. Before entrance to the hospital the patient was seen twice at her home, the first time being twelve hours after the onset of generalized abdominal discomfort with slowly increasing nausea. The temperature was 98.4° F., the pulse rate was 86, and the blood pressure was 176 systolic and 108 diastolic. Examination showed moderate generalized abdominal tenderness and a nodular tender mass the size of an orange in the lateral portion of the right upper quadrant just below the costal margin. Noted also was a patchy vesiculopapular eruption on the palms and a papular purpuric eruption on the inner aspects of the soles, these lesions having started four or five weeks before. Six hours later all the symptoms were increased, vomiting of bile had occurred twice, the temperature was 99° F., and the mass was slightly larger, smoother, and more tender. The clinical diagnosis was inflammatory tumor of the right upper quadrant of uncertain origin, hypertension, possibly transient, and dermatitis medicamentosa from empirin compound. Hospitalization was advised for surgical treatment.

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Physical examination at the time of the patient's admission to the hospital showed that she was well developed and well nourished. She was suffering rather severe pain. The temperature was normal, the pulse rate was 84, and the blood pressure was 174 systolic and 108 diastolic. The heart was of normal size, but a blowing systolic murmur was heard over the entire precordium. There was generalized tenderness over the abdomen, with the maximum tenderness in the right upper quadrant, just below the costal margin. The white blood cell count was 27,700, with 73 per cent polymorphonuclears, 5 per cent staff forms, 8 per cent lymphocytes, and 14 per cent monocytes. The blood cholesterol value was 147 mg. per hundred cubic centimeters, and the icteric index was 6.9. Twelve hours after admission the white blood cell count was 29,000.

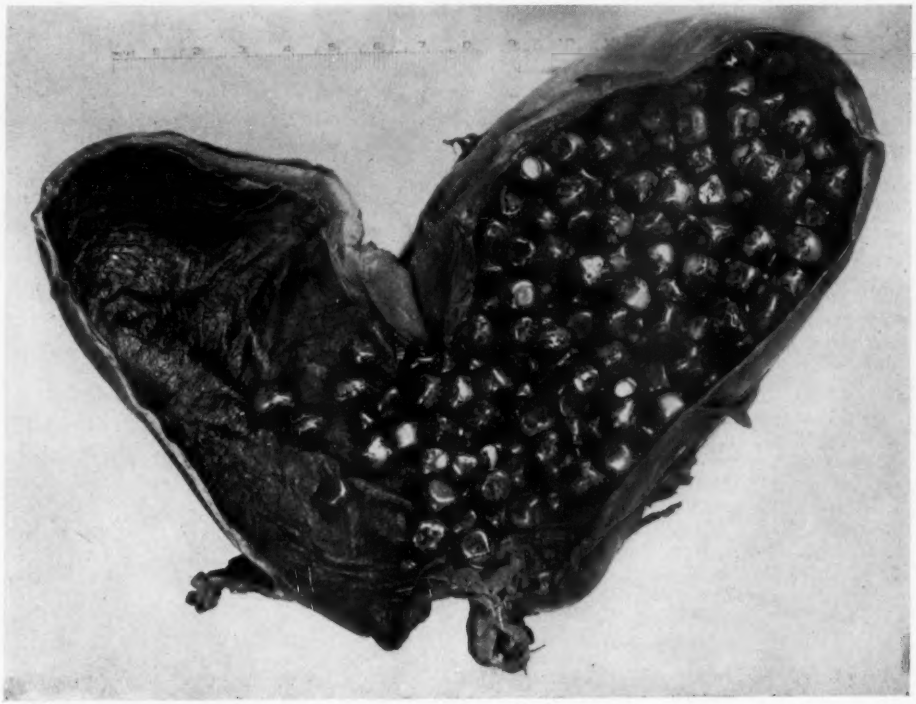

Fig. 1.—Gross specimen of infarction of the gall bladder.

A clinical diagnosis of acute cholecystitis was made, and on March 27 cholecystectomy was done. The abdomen was opened by a right rectus incision, and an enormously distended gall bladder was immediately presented. For the most part it was a blackish brown, and at one point a small tag of omental tissue was lightly adherent. The gall bladder was quickly removed from the fundus downward, the cystic duct and the cystic vessels being ligated separately. The wound was closed in layers around a cigarette drain.

The postoperative course was satisfactory, except for a persistently rapid pulse rate, until March 30, the third postoperative day, when the patient began suddenly to complain of palpitation and clammy perspiration. Examination revealed a grossly irregular cardiac rhythm, with the apical rate 120 to 160 and the radial rate 90 to 100, a pulse deficit of 20 to 60. An electrocardiogram made at this time was characteristic of auricular fibrillation with a rate of 250. Treatment with digitalis was started immediately but was discontinued after several hours because of the advent of ventricular extrasystoles. Quinidine was given, and the pulse became regular, but this medication also had to be stopped, in this case be-

cause of nausea. However, fibrillation did not recur. An electrocardiogram made on April 2 revealed sinus mechanism interrupted occasionally by ectopic nodal and ventricular beats. The convalescence was uneventful from that time on, and the patient was discharged from the hospital on April 12, the sixteenth postoperative day. The subsequent course has been satisfactory.

The report on the pathologic specimen was as follows:

Gross Description.—The gall-bladder was huge, weighing 580 Gm. and measuring 16 cm. in length. Twenty-one millimeters of cystic duct were attached. The external circumferences were as follows: corpus, 26 cm.; fundus, 25.5 cm.; and neck, 12 cm. The hepatic surface measured 12 by 8 cm. Most of the free serosal surface was smooth and light to dark red, but the corpus and neck were covered with an oblique strand of fatty adhesions attached for a distance of 11 cm. and measuring 3 cm. in length. The lumen contained 200 ml. of dark green bile, 300 (by actual count) faceted cholesterol stones up to 12 mm. in diameter, and myriads of smaller concretions 1 to 2 mm. in diameter. The dark red wall varied in width from 3 to 10 mm. The serosa and mucosa separated spontaneously when the gall bladder was opened. The dark green mucosa was smooth except for several submucosal linear strands. No infection or ulceration was noted.

Microscopic Description.—The various sections showed practically no viable structures. The wall was converted into a swollen, pale pink, ghostlike structure with linear zones of polymorphonuclear leucocytes beneath the serosa. There was extensive erythrocytic extravasation throughout. There was no involvement of the cystic artery. The cause of the infarction could not be determined from examination of the specimen.

Diagnosis.—Hemorrhagic infarction of the gall bladder; cholecystolithiasis.

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FAILURE TO RECOVER SULFONAMIDES FROM GALL BLADDER BILE IN DOGS WITH CYSTIC DUCT OBSTRUCTION

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IT HAS been demonstrated that sulfonamides are excreted in the bile in man and in certain laboratory animals,[1-4, 6, 8, 9] and there is clinical evidence that these drugs exert a beneficial effect in some biliary tract infections.[1, 4, 5, 8] On the other hand, in many cases of biliary tract disease there is no benefit from the drugs, and, as Watson and Spink[10, 11] have shown, hepatic injury actually may be produced, particularly after the administration of sulfanilamide. In our clinic, observation of several patients with acute obstructive cholecystitis has indicated that the administration of sulfonamides in such cases does not alter the course of the disease. Therefore, it is desirable to learn whether obstruction of the cystic duct prevents these drugs from entering the gall bladder, or whether they can reach the gall bladder bile through the vesical wall. This study was undertaken to secure information regarding that question.

METHOD OF EXPERIMENTATION

The experiments were carried out upon twelve healthy adult dogs. Under ether anesthesia and with aseptic surgical technique the cystic duct was isolated and ligated without injury to the blood supply of the gall bladder. The following day, when the animal had recovered from the operation, one of the sulfonamide drugs was administered by mouth (sulfanilamide, sulfathiazole, and sulfadiazine were used). In some cases the drug was administered in a single dose, in other instances in divided doses (see Tables I and II). The animal was sacrificed later,

TABLE I

DOG NO.	WEIGHT (KG.)	DRUG	DOSE*	SULFONAMIDE IN GALL BLADDER BILE	GROSS APPEARANCE OF GALL BLADDER	MICROSCOPIC APPEARANCE OF GALL BLADDER
111	11	Sulfanilamide	1 dose 8 Gm.	None	Normal	Normal
115	13	Sulfathiazole	1 dose 8 Gm.	None	Normal	Normal
117	16	Sulfadiazine	1 dose 8 Gm.	None	Normal	Normal

*Sacrificed seven hours after drug was administered.

*Captain in U. S. Army with U. S. General Hospital No. 26.

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TABLE II

DOG NO.	WEIGHT (KG.)	DRUG	DOSE	GALL BLADDER ANALYSIS	VENOUS BLOOD ANALYSIS (MG. % FREE SULFONAMIDE)	GROSS APPEARANCE OF GALL BLADDER	MICROSCOPIC APPEARANCE OF GALL BLADDER
126	6	Sulfanilamide	1 dose 4 Gm., sacrificed 4 hr. later	No sulfanilamide	45.9	Normal	Normal
128	6	Sulfathiazole	1 dose 40 gr., sacrificed 4 hr. later	No sulfathiazole	9.1	Normal	Normal
132	7	Sulfadiazine	2 doses of 5 Gm. each, sacrificed 6 hr. later	No sulfadiazine	10	Normal	Normal
133	6	Sulfathiazole	As above	No sulfathiazole	10	Normal	Normal
134	5	Sulfanilamide	As above	No sulfanilamide	45	Normal	Normal
135	8	Sulfanilamide	As above	No sulfanilamide	62	Normal	Normal
136	18	Sulfanilamide	2 Gm. b.i.d. x 2 days, 2 Gm. 4 hr. before sacrifice	No sulfanilamide	15.8	Normal	Normal
137	16	Sulfanilamide	As above	No sulfanilamide	18.2	Normal	Normal
138	18	Sulfanilamide	As above	No sulfanilamide	15.8	Normal	Normal

and the level of the sulfonamide in the gall bladder bile and in the venous blood was determined. Doubilet's method of analysis, as described by Carryer and Ivy,[3] was used for the bile, and the procedure of Marshall and Litchfield[7] was used for the blood. The gall bladder wall was examined grossly and microscopically to dismiss the possibility of disturbance of the blood supply.

RESULTS

In each case, examination of the dog at the time of completion of the experiment showed that the ligature obstructed the cystic duct without interfering with the blood supply of the gall bladder. Gross and microscopic examination of the gall bladder wall confirmed the fact that its blood supply had not been disturbed. Sulfonamide was not found in any of the specimens of gall bladder bile (see Table II), in spite of high blood levels. In these experiments, obstruction of the cystic duct prevented sulfanilamide, sulfathiazole, and sulfadiazine from entering the gall bladder.

SUMMARY

It is well known that the sulfonamides are excreted in the bile in man and in animals. Furthermore, Bettman and Spier[2] have demonstrated that these drugs are concentrated in a gall bladder which functions normally. Our experiments show that sulfanilamide, sulfathiazole, and sulfadiazine do not enter the gall bladder of the dog when the cystic duct is occluded. They do not pass through the wall of the vesicle to reach the gall bladder bile.

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SERUM SICKNESS SIMULATING ACUTE ABDOMINAL DISORDERS

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SEVERE abdominal pain, as Duke[1] has aptly pointed out, is a symptom which is never taken lightly by a careful physician. It often indicates a severe illness; in fact, it often indicates an emergency. However, abdominal pain which may simulate in some respects the pain caused by severe abdominal disease is occasionally the result of hypersensitiveness to a foreign serum. Abdominal pain sometimes occurs without other manifestations of serum sickness, or rather, it may be the sole striking symptom of serum allergy. In such a case, the real cause of the pain may not be apparent and an error in diagnosis can easily be made. Although cases have been reported in which an allergic state has simulated the acute abdomen, these have been due to ingestants, and we have been able to find none in which the responsible agent was parenterally administered prophylactic or therapeutic sera. In view of the increasing use of such sera in civil as well as military life it is felt that the recognition of the abdominal features of serum sickness will become of progressively greater importance.

Our illustrative cases have been selected from a larger number and represent typical histories of patients who have abdominal pain as the outstanding symptom of serum hypersensitivity.

CASE REPORTS

CASE 1.—C. H., a 17-year-old colored male, was admitted to the observation ward stating that he had been seized with a severe abdominal pain two hours previously. There was no nausea, vomiting, or loose stools. There had been no previous history of indigestion. Physical examination revealed generalized rigidity of the abdomen. The temperature was 100° F. There were 9,500 white blood cells, 91 per cent neutrophiles, and 9 per cent small monocytes. The urine was negative. The possibility of a perforated viscus was entertained and the patient was x-rayed to rule this out. The pain was so excruciating that although ⅙ gr. morphia had been administered to relieve apprehension, severe discomfort necessitated the administration of a second dose of the drug. The patient was prepared for operation. An ice-cap was applied to the abdomen and the patient was kept in the observation room overnight. At seven o'clock in the morning it was noticed that the patient had a generalized urticaria associated with marked itching. It was then learned that he had received antitetanic serum for a dog bite three days previously. The urticaria and pruritus responded to the administration of epinephrine and the application of calamine lotion.

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CASE 2.—A. D., a 14-year-old colored male, was admitted to the surgical service with a chief complaint of abdominal pain. Three days prior to admission the boy began to experience crampy pain in the umbilical region. This was associated with nausea but not vomiting. On the day of onset of the abdominal pain the patient had several loose bowel movements.

Physical examination was essentially negative except for the abdominal findings. The abdomen was symmetrical; there was tenderness in the right lower quadrant. There was no rigidity.

There were 10,300 white blood cells, 72 per cent polymorphonuclears, 12 per cent lymphocytes, 6 per cent monocytes, and 10 per cent eosinophiles. Despite the absence of rigidity the patient was placed on surgical liquids and prepared for exploratory laparotomy. In the interim typical urticarial wheals appeared. These wheals and the abdominal symptoms responded promptly to the administration of ephedrine.

Questioning then revealed that the patient had received antitoxin for a laceration of his hand the previous day. It may be assumed, therefore, that the patient suffered from an accelerated serum reaction.

DISCUSSION

To gain an understanding of present concepts of serum sickness, it is necessary to look back to the work of Richet[2] and his collaborators that was done at the turn of the present century. Richet, while sojourning on the yacht of the Prince of Monaco in the Indian Ocean, undertook the study of the urticating principle of the Portuguese man of war, a variety of sea nettle or stinging jellyfish. He considered the urticating principle a toxin and injected into dogs extracts made from these nettles. To his surprise he found that although the first injection was harmless, the second injection made some days later provoked severe, and at times, fatal reactions. He considered that the first injection removed the animal's natural immunity to this toxin, hence a state of anaphylaxis existed. This was not the correct explanation; it would have remained an academic question, however, had not the introduction of diphtheria antitoxic sera by von Behring[3] produced in humans a state strikingly parallel to the anaphylactic animal.

A completely satisfactory explanation of serum sickness eludes us even today. Certain facts, however, are known; thus, during and following serum disease induced by the injection of immune animal serum, circulating antibodies may be found in the blood. These antibodies are not constant but vary quantitatively and qualitatively in different cases. They include precipitans (anaphylactic antibodies), heterophile antibodies, and atopic reagins. Precipitins are frequently found in the blood of human beings following the administration of immune animal serum, but such precipitins may occur without the development of serum disease. Furthermore, they are regularly absent in the blood of patients treated with normal horse serum even in the presence of typical serum sickness (Harten and Walzer[4]). Atopic reagins (Prausnitz-Küstner or skin-sensitizing antibodies) occur frequently but by no means regularly following the administration of therapeutic serum. Heterophile antibodies

(hemolysins and agglutinins for sheep red blood cells) occur in the blood after serum has been given. An analysis of all the available data still fails to reveal a constant association of any type of antibodies with serum sickness. One is compelled to conclude with Harten and Walzer that the mechanism of serum sickness cannot be correlated with any of the antibodies which have thus far been detected in this condition. Indeed Coca's[5] theory that the symptoms of serum disease are due to specific altered reactivity of the protoplasm of some of the body cells which is not mediated by antibodies has not yet been controverted.

Perhaps the major phenomena of serum sickness are due, as Foshay and Hagebusch[6] suggest, to a release of histamine or a histamine-like substance into the circulation consequent on the union of serum protein antigen and antibodies. Certainly the brilliant experimental work of Katz[7] demonstrates clearly that histamine is intimately concerned with the production of the allergic state; many gaps in our knowledge of the exact role of histamine (or similar substances) remain to be filled in. Regardless of the precise nature of the underlying mechanism, the pathology of the allergic or anaphylactic state seems to be fairly well agreed upon. Contraction of smooth muscle, capillary dilatation with edema, and diapedesis of red cells (which may progress to hemorrhage) and eosinophilic infiltration in one or another combination produce the signs and symptoms which are recognized clinically and experimentally.

It is not clear why certain tissues or organs should be affected in serum disease to the exclusion of others; it is known, however, that they may be locally sensitized or more highly reactive than others. That this local sensitivity was on a cellular rather than a humoral basis has been demonstrated by experimental work. Friedmann[8] and Otto[9] as well as Doerr[10] showed that in the process of passive sensitization, in which the blood of a sensitized guinea pig is transferred into a normal nonsensitive guinea pig, the latter does not become sensitized until after an interval of at least four hours. Indeed, twenty-four to forty-eight hours must elapse before maximum passive sensitization has been accomplished. This interval is required presumably for the antibodies to be firmly attached to the tissue cells (Vaughan[11]). Schultz[12] found that if, after the first injection of foreign serum, a long enough interval elapsed, intestinal muscle would show a supranormal degree of irritability toward the same serum. After washing strips of sensitized intestinal smooth muscle free from blood he found that contact with the specific antigen caused an anaphylactic response with muscular contraction. Dale[13] improved on the Schultz technique, developing the uterine strip method which has since become a routine procedure in the study of sensitization.

That other abdominal viscera may partake of the general sensitization has been demonstrated in the instance of the gall bladder by Deissler and Higgins.[14] Strips and isolated whole gall bladders from guinea pigs previously sensitized to horse serum and egg white were found to react

strongly to the addition of the antigen. The gall bladder contracted during shock but the sphincter contracted to a greater extent, thus no emptying occurred. Hence we have a type of biliary colic on a dyskinetic mechanism. Couvelaire and Bargeton[15] sensitized dogs to horse serum by intravenous administration; on re-exposure to the antigen by injection of serum into the duodenopancreatic vein and directly into the pancreas itself, although no general shock resulted, an immediate local persistent edema of the pancreas became apparent. When the animal was sacrificed the next day the peritoneal cavity was found to contain serosanguineous fluid and on the omentum were several whitish areas having the appearance of fatty necrosis. The pancreas was edematous and contained multiple hemorrhages. One cannot but be struck by the similarity of these lesions to those found in acute hemorrhagic pancreatitis. It is well known that in about one-half the cases a stone in the ampulla of Vater leads to a diversion of bile into the pancreatic ducts. According to Bloomfield[16] no anatomic reason for entry of abnormal material into the pancreatic ducts can be demonstrated in many instances. We suggest that these cases of acute hemorrhagic pancreatitis may represent a fulminating type of allergic reaction.

Granted that these lesions may be demonstrated in the experimental animal, the question may fairly be asked whether similar conditions have been observed in the human being. Speaking of the gastrointestinal tract in angioneurotic edema, Osler[17] stated that ten of his patients had colic; he considered that the nature of the local trouble was known, as exploratory operations confirmed his view that it was an edema of the wall of the bowel. In a case reported by Morris,[18] in washing out the stomach to relieve the severe vomiting, a portion of the mucosa was removed and on examination was found to be in a state of acute edema. Osler described the colic of intestinal angioneurotic edema with great clarity. In his experience it came on suddenly and often reached an extreme grade. As a rule it occurred with the skin manifestations, but at times it was the only feature, and often there was no clue as to the nature of the trouble. In the majority of cases the pain was central, more or less continuous with paroxysms of greater intensity. The patient tended to roll about in bed or be doubled up in an agony of pain. The abdominal walls were tense; appendicitis, gallstone, or renal colic were suspected and in a considerable number of his cases laparotomy was performed. In severe attacks vomiting occurred with the pain and lasted many hours. The patient looked very ill, with pallor, small pulse, and features of collapse; at the end of ten or twelve hours the symptoms often disappeared, an outbreak of local edema giving a hint concerning the diagnosis. He noted that with gastric symptoms and colic there sometimes occurred diarrhea, meteorism, and even the passage of blood.

A case reported by Bogart[19] is of especial interest. The patient presented the picture of a very severe illness requiring operative relief.

The abdomen having been opened, the jejunum was found to be quite swollen and edematous. This swelling and edema extended up to the point where the intestine passed beneath the mesentery and was so pronounced as to produce a stiffening of the intestine sufficient to prevent peristalsis; when grasped between the forefinger and thumb the intestine was apparently at least one inch in thickness. Evidently the lumen was almost if not entirely occluded. The patient gradually convalesced after the operation, recovering after seventeen days.

Alexander and Eyermann[20] have expressed the opinion that there seems to be a close relation between Henoch's purpura and acute intestinal allergy due to the ingestion of foods; in both, spasm of portions of the intestinal musculature is demonstrable with the x-ray, and peritoneal urticaria and hemorrhage with edema of the bowel wall are demonstrable on laparotomy. In describing the symptoms of Henoch's purpura, Piness and Miller[21] state that not infrequently it closely simulates the acute abdomen.

The treatment of the acute abdominal crisis due to serum sickness is the treatment of the latter condition generally, namely the exhibition of the sympathomimetic drugs. It is necessary, of course, that a diagnosis be made; where skin or joint manifestations are concomitant, the situation is obvious at a glance, where this is not the case the presence of recent wounds treated prophylactically with antitetanic serum, or a history of recent illness treated with therapeutic sera should give one the clue to the true state of affairs.

SUMMARY

Case reports of serum disease simulating the acute abdomen are presented. Possible etiologic mechanisms drawn from a brief survey of experimental and clinical publications are given.

In view of increasing prophylactic and therapeutic use of sera it is felt that recognition of the abdominal features of serum sickness will be of progressively increasing importance.

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Editorial

Dicoumarin and Prophylactic Anticoagulants in Intravascular Thrombosis

THAT cattle are sometimes affected by a hemorrhagic disease which seems to develop for no apparent reason and is occasionally fatal has long been common knowledge among veterinarians and cattle raisers. However, it was not until relatively recently that the explanation for this phenomenon was given by two veterinarian investigators, Schofield, in Canada, and Roderick, at the North Dakota Agricultural Experimental Station. Their studies showed conclusively that the disease was due to the eating of improperly cured hay or spoiled sweet clover silage and the condition became known as sweetclover disease of cattle. In 1934, Professor Karl Paul Link and his associates, of the Wisconsin Agricultural Experimental Station at the University of Wisconsin, became interested in this phenomenon and began experimenting to determine the causal factor of hemorrhage in the spoiled fodder. Seven years later, these carefully conducted and brilliantly conceived series of investigations were culminated with the isolation and synthesis of the hemorrhagic agent in spoiled sweet clover, dicoumarin, 3,3′-methylene-bis-(4-hydroxycoumarin), a white crystalline substance readily soluble in alkaline solutions but only slightly soluble in water.

Intensive studies have since been undertaken to determine the pharmacologic and therapeutic action of dicoumarin. Accordingly, it has been found that the principal effects of dicoumarin are prolongation in prothrombin time and delay in coagulation of blood. Following its administration, either orally or intravenously, a variable lag period of from twenty-four to seventy-two hours exists before this action becomes manifest. Although there is some evidence to support the belief that dicoumarin produces physiologic inhibition of prothrombin formation in the liver, or destruction or suppression of prothrombin activity, its exact mechanism of action has not been definitely established. Apparently, orally or intravenously administered vitamin K produces little or or no effect on the hypoprothrombinemia or on the hemorrhagic manifestations which follow the use of dicoumarin. Indeed, it would seem that this can be influenced only by means of transfusions of fresh whole blood or plasma. Other studies have shown that dicoumarin has a tendency to impair clot retraction and increase the sedimentation rate of erythrocytes, but it seems to produce no significant changes in erythro-

cyte or leucocyte counts, in the fragility of erythrocytes and blood platelets, in the hepatic and kidney functions, and in the values for nonprotein nitrogen, blood sugar, bilirubin, and calcium in the blood. Prolonged excessive doses of dicoumarin almost invariably result in fatal hemorrhage, but no significant pathologic changes except those due to bleeding into the tissues have been found on necropsy studies.

The anticoagulant property of dicoumarin forms the basis of its therapeutic significance. Accordingly, its obvious theoretic value clinically would be in the prophylaxis of intravascular thrombosis. Heparin, which has the disadvantages of being costly, requiring continuous or repeated intravenous injections, and of maintaining a constant anticoagulant effect with difficulty, has been the most recently developed and widely heralded agent for this purpose. If dicoumarin could be shown to be as good as, or superior to, heparin in this respect, it would have a decidedly practical advantage. Workers interested in blood and peripheral vascular diseases, therefore, eagerly seized upon this new anticoagulant agent and began studies to evaluate its clinical efficacy in the prophylaxis and treatment of postoperative thrombosis and phlebitis, pulmonary embolism and infarction, coronary thrombosis, and peripheral vascular disease. The results of these preliminary studies have appeared in recent issues of current journals. Allen and his co-workers, at the Mayo Clinic, administered dicoumarin in 374 cases "in an effort to prevent arterial or venous thrombosis and pulmonary embolism or to prevent extension of intravascular thrombosis." Three of these patients developed clinical thrombosis in spite of the fact that the prothrombin time was elevated. Accordingly, the authors concluded that these observations and their experimental studies "strongly suggest the value of administering dicoumarin in preventing intravascular thrombosis." Somewhat similar studies and conclusions were also reported by other observers.

Several considerations may be introduced to support the cautious position of provisional reluctancy in accepting these conclusions. Notwithstanding certain implications, the statistical significance of the reported results upon which many of the conclusions are based is open to question because the series of investigations is not adequate nor are the results sufficiently impressive to justify definite statements. This is clearly demonstrated by a comparison with other incidences of postoperative thrombosis in cases not receiving anticoagulant prophylactic measures. Thus, in a series of 4,410 consecutive operations performed at the Charity Hospital, in New Orleans, exclusive of procedures on the eye, ear, nose, and throat, there were only 3 (or 0.06 per cent) cases of postoperative thrombophlebitis. Even more significant is the fact that better results have been reported following the use of much simpler, safer, and more economical prophylactic measures than the administration of dicoumarin or other anticoagulant agents. Thus, Zava, using early ambulation

postoperatively, reported over 6,000 surgical cases, many of which were gynecologic, without a single occurrence of embolism. In addition to these considerations is the fact that dicoumarin, like other anticoagulants, possesses certain hazardous features. Of these, the most important is hemorrhage, which in surgical cases obviously assumes even greater significance. Hemorrhage occurred in 31 cases in the series reported by the Mayo investigators, 24 of which occurred from the operative site; 1 was fatal. There were 2 other fatal cases apparently as a result of hemorrhage in patients with subacute bacterial endocarditis. The authors believe that dicoumarin is contraindicated in such cases, because in these patients there is apparently an increased tendency to bleed. Attention is also directed to certain other conditions in which the drug should be employed cautiously or not at all. These include renal insufficiency or those with an already prolonged prothrombin time, such as obstructive jaundice or other vitamin K deficient diseases. The fact that there exist wide and as yet unexplained variations in the prothrombin and hemorrhagic response to dicoumarin in different individuals, emphasizes further the practical significance of these jeopardous features.

It becomes apparent from these considerations, therefore, that, for the present, dicoumarin cannot be regarded as a safe, efficacious, and satisfactory prophylactic or therapeutic agent in intravascular thrombosis. In recent years, there has been a revival of interest in the use of anticoagulants for this purpose. Until the arrival of dicoumarin, heparin had received the most assiduous attention and intensive efforts of investigators in this field. The fact that workers are already seeking a substitute demonstrates clearly that heparin did not prove completely satisfactory. In the prophylaxis and treatment of intravascular thrombosis, certain difficulties and objectionable features must be overcome before any anticoagulant can be considered entirely satisfactory and its use become widely adopted. The prophylactic value of any anticoagulant agent is manifestly difficult to establish in such notorious unpredictable conditions as intravascular thrombosis. Further emphasis is placed upon the undesirability of this particular characteristic by the fact that the anticoagulant agent must be employed in all cases, which is obviously impractical. This is especially true in view of the danger of hemorrhage which may follow the use of an anticoagulant agent and which assumes obvious significance in surgical cases. Therapeutically the use of an anticoagulant in intravascular thrombosis has at least the theoretical objection of increasing the tendency of embolism. That this is not entirely theoretic, however, is shown by our experience with a patient, who, while heparinized over a period of four weeks, had five nonfatal emboli. Obviously in such cases the more certain means of preventing propagation of the thrombus or embolization is by proximal vein ligation. In view of the present lack of trenchant knowledge con-

cerning the etiologic factors in intravascular thrombosis the rationale of anticoagulants as combative measures may be justifiably questioned. These protesting considerations to the prophylactic and therapeutic use of all anticoagulants in intravascular thromboses are not intended as critical disapprobation but rather as criticism in its strict etymologic sense, that is, evaluation. A restatement of facts is frequently necessary to dispel the fog of enthusiasm and thus permit a clear discernment of objectives.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

AMEBIC HEPATITIS AND HEPATIC ABSCESS

AN ANALYSIS OF 181 CASES WITH REVIEW OF THE LITERATURE

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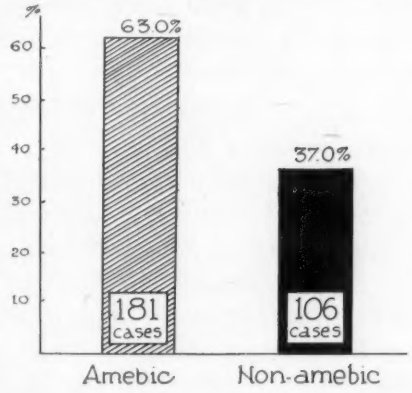
IN PREVIOUS publications we[277, 287] presented an analysis of 73 patients with amebic hepatitis and hepatic abscess, admitted to the Charity Hospital and the Touro Infirmary during the six-year period, 1928 to 1933 inclusive, and 66 patients admitted to these institutions during the four-year period, 1934 to 1937 inclusive. Since then, i.e., during the four-year period 1938 to 1941 inclusive, there have been 42 cases of amebic hepatitis and hepatic abscess.[285] During this fourteen-year period there have been 287 patients with liver abscess admitted to the Charity Hospital and Touro Infirmary in New Orleans and of this number 181 (63 per cent) were amebic and 106 (37 per cent) were nonamebic (Graph I). Whereas the present report is based upon a study of the total number, 181 patients admitted during the fourteen-year period, 1928 to 1941 inclusive, significant comparisons of the three groups will be considered wherever desirable. In addition to this an attempt has been made to review the literature and present a comprehensive survey of the subject. While the literature was reviewed up to 1937 in a previous publication, in the present report this is brought up to date and for purpose of convenience and because of the relative inaccessibility of the previous publication much of this material is included.

History.—A historical consideration of amebic hepatic abscess must necessarily include that of amebic dysentery. Whereas knowledge concerning suppurative disease of the liver has existed since the time of Hippocrates and perhaps earlier, the realization of amebic hepatic abscess as a separate clinical entity is of relatively recent origin. In a comprehensive exposition of the subject, Bertrand and Fontan[21] presented an excellent historiographic résumé of the former. The causal relationship between amebic dysentery and amebic abscess was considered as early as 1818, by Ballengal[10] and later by Annesley,[6] Budd,[37] Dutroulau,[106] and others even before the ameba was described, but its true character was not established until after the causal agent of amebic dysentery was recognized.

During this early period it appears that the relationship between dysentery and hepatic abscess was recognized especially by the observers in India, whereas most European investigators did not consider it significant. In his consideration of liver abscess occurring in India, Annesley, in 1828, directed attention to the frequent association of these two conditions and accurately described the ulcerative lesion in the large bowel. Although he realized the difficulty of establishing an etiologic relationship, he expressed his conviction that "abscess of the liver is in some cases consequent on dysentery, and caused by it," a conclusion reached by Budd in his investigations of the subject twenty-five years later. This subject, however, remained controversial for many years later and even after the isolation of the ameba. Frerichs,[129] the eminent German pathologist and internist, severely criticized the views held by Annesley and Budd and stated, in 1879, that, "It has been far too generally assumed that the dysentery precedes the hepatic inflammation; almost all physicians who have acquired their experience in warm



Graph I.—Relative incidence of amebic and nonamebic hepatic abscesses in 287 patients admitted to Charity Hospital and Touro Infirmary during the 14-year period, 1928 to 1941, inclusive.

climates have arrived at the conviction that the dysentery is often preceded by the hepatitis, or that the two may be developed simultaneously, and that hepatitis frequently occurs without any disease of the intestine." He states further that "a careful analysis of cases of this nature is entirely opposed to the idea of their connection with intestinal ulceration. Moreover, as regards the cases where the dysenteric ulceration of the intestine has preceded the development of the abscesses of the liver, it has not yet been proved that the hepatic disease is the result of the intestinal infection, and, above all, no one has succeeded in demonstrating, as the connecting link, any implication of the roots of the portal vein in the intestinal inflammation, or an intestinal pylephlebitis." These disputations were continued as late as 1898 and Rogers,[325] in his Lettsonian Lectures, directs attention to the "completely contradictory statements in the articles on dysentery and liver abscess in the first edition of Allbutt's System of Medicine by Davidson and

Lafleur respectively.'' The former author[93] considered liver abscess occurring in tropical or subtropical countries as ''an uncomplicated disease, and that when complicated with dysentery it not infrequently precedes it'' and contended that it was due to a primary hepatic insufficiency consequent to residence in a hot climate which ''favors the settlement and growth of pyogenetic organisms in the liver, quite apart from any dysenteric complications . . .'' In contradistinction to this hypothesis, Lafleur[204] described clearly the pathogenesis of amebic dysentery and its complication, hepatic abscess, and attributed the process to the direct activities of the ameba. Even up to the turn of the present century the subject remained controversial and as expressed by Rogers,[325] ''in spite of the valuable work, especially by Kartulis and Councilman and Lafleur, medical opinion in 1902, particularly in India, was against the recognition of amebic dysentery as a distinct disease and also to a great extent contrary to its acceptance as the causative agent of tropical liver abscess, while there were still great differences of opinion as to whether such abscesses were in any way directly associated with dysentery.''

Credit for the discovery of the *Endameba histolytica* is usually given to Lösch,[214] (1875). However, it should be realized that although he successfully reproduced the disease in one of four dogs by contaminating their food and injecting them rectally with stools containing the motile amebae, he did not consider the ameba as the cause of the disease but merely suggested that their presence delayed healing of the ulcerations. Koch,[197] in 1883, stated that he had observed amebae in material obtained from colonic ulcers of five patients dying of dysentery in Egypt. Two of these cases were complicated with liver abscess, and because in one amebae were found in the capillaries and tissues adjoining the abscess, he considered their possible etiologic significance. Perhaps Kartulis[191] presented one of the most important early contributions toward the recognition of the etiology of amebic dysentery and its complication, liver abscess. In 1886, he published the results of his investigation of 150 cases of dysentery in Egypt. He demonstrated amebae, similar to those previously described by Lösch, in ulcers and in tissue beneath ulcers of sections of diseased intestines, and concluded that these protozoa were the cause of ''tropical dysentery.'' He stated subsequently[192, 193] that he had found similar amebae in the pus of liver abscesses and that it was the causal agent of hepatic abscess associated with dysentery in the tropics. As stated previously, in viewing retrospectively the then current controversy which apparently raged concerning the etiology of ''tropical dysentery'' and associated liver abscess, it is of curious interest, in the light of subsequent development, to read the severely critical attack of Kartulis' conclusions launched by Bertrand and Fontan[21] in their extensive treatise published in 1895, and the argumentative defense of their view that liver abscess associated

with dysentery is caused primarily by invasion of pyogenic microorganisms and that amebae might play a secondary but not a specific role.

Numerous investigators subsequently confirmed Kartulis' observations. One year after Kartulis' publication, Jaroslov Hlava[165] demonstrated amebae in sixty cases of dysentery occurring in Prague and successfully reproduced the disease in four of six cats by intrarectal inoculation of dysenteric stools obtained from human beings. In this connection there is an interesting and rather curious story which has medico-literary significance. For over fifty years these observations of Hlava were credited in textbooks and periodicals on the subject, to "Dr. O. Uplavici."[379] Several years ago Dobell[101] unmasked this mysterious character. It appears that Hlava[165] published his original article in a relatively inaccessible Czechoslovakian journal with the title, "O Ůplavici. Predbezné sdeleni" (On Dysentery. Preliminary Communication). According to Dobell no translation or further communication was ever published and subsequent investigators have referred to the brief review or abstract of this article signed by Kartulis and appearing in the *Centralblatt für Bakteriologie und Parasitenkunde.*[379] Extraordinary as it may seem, Hlava's name was completely omitted in this abstract and only the title of his paper was presented as "Uplavici, O."[379] Moreover, not only did Kartulis refer to the author personally as Uplavici but in the contents of the issue in which the abstract appears the name is given as "Uplavici, O." By 1910, "Uplavici, O." was listed in the *Index Catalogue of Medical and Veterinary Zoology,* as having acquired a doctor's degree. As stated by Dobell, the mysterious "Dr. O. Uplavici" has haunted respectable books and periodicals long enough and it "seems high time that this ghost should be laid once and for all."

Of no less historical importance are the investigations in this country. Osler,[291] in 1890, observed amebae in a liver abscess of a patient operated upon and in whom amebae were found subsequently in the stools. Shortly afterward, similar observations were made by Stengel,[356] Musser and Willard,[263] and Dock.[103] In 1891, Councilman and Lafleur[70] presented their classical contribution based upon a perspicuous investigation of fifteen cases of amebic dysentery and six complicating liver abscesses. These studies conclusively established "amebic dysentery" and its complication "amebic abscess of the liver" as clinical entities with the ameba as the specific etiologic agent. Indubitable corroborative evidence of this fact was supplied by Kovács,[200] in 1892, who successfully produced dysentery in kittens with amebae from dysentery cases in human beings, and by Kruse and Pasquale,[201] in 1894, who successfully produced characteristic dysentery in a cat by intrarectal instillation of sterile liver abscess pus containing amebae. In 1901, Harris[155] also accomplished, perhaps for the first time in puppies, successful experimental production of amebic hepatic abscess following experi-

mentally produced amebic dysentery. Subsequently, similar results were obtained in cats by Craig,[76] Huber,[181] and others.[9, 91, 391]

The important extensive clinical investigations of amebic hepatic abscess by Sir Leonard Rogers deserve mention in any historical consideration of the subject. Approximately four decades ago[320] this investigator demonstrated that whereas active amebae were frequently not present in the "pus" they were constantly found in the wall of tropical abscesses of the liver and that in the majority of instances pyogenic organisms were absent from these abscesses when they were first opened. He immediately realized the significance of this fact and directed attention to the importance of treating the abscesses conservatively with aspiration and emetine, which will be considered in greater detail under the discussion of therapy. Of interest in this connection is a recent article of Huard, Long, and Graziana[171] in which a Dr. Florence[125] is cited as antedating Rogers in the use of emetine therapy. They state that Dr. Florence employed hypodermic injections of emetine as early as 1882.

Incidence.—Intensive studies during the past decade have clearly established the relative frequency and increasing significance of amebiasis. In spite of the well-established fact that amebiasis is of ubiquitous occurrence, the fallacious impression still exists that amebiasis is an acute disease usually contracted in the tropics and manifested principally by dysentery or liver abscess. Its universal distribution has been conclusively demonstrated by extensive surveys made in various parts of the world. As aptly expressed by Faust,[118] "*Endamoeba histolytica* has been found wherever careful coprological surveys have been made on the human population, from Saskatchewan, Canada (52° 30′ N.) to the Strait of Magellan (52° S.)." Its prevalence in the United States has been emphasized repeatedly by Craig[72] who is of the opinion that between 5 and 10 per cent of this country's population harbor the parasite. That this is not an exaggerated estimate is clearly demonstrated by the results of numerous surveys in various parts of the country. Indeed, on the basis of more recent investigations Faust[118] concludes that "the incidence figure may possibly average as high as 20 per cent, or double that of previous accepted estimates." As early as 1911, Sistrunk[347] directed attention to its frequency here and found it present in 17.2 per cent of 145 patients examined at the Mayo Clinic. Subsequent studies in this institution revealed an incidence of 22.5 and 7.9 per cent, respectively.[228, 338] In the Veterans Bureau Hospital in California, Wight[393] observed an incidence of 6.8 per cent and Meleney, Bishop, and Leathers[244] found it to be 11.4 per cent in an examination of 20,237 individuals in Tennessee. Faust[114] reported a 20 per cent incidence in one county in Virginia and 13.7 per cent in an examination of 1,100 individuals in New Orleans. Craig[83] found a 12.7 per cent incidence in an examination of 189 officers of the Medical Corps of the United States Army. In 1934, Craig[85] reported the results of a collection of the most important surveys made in various

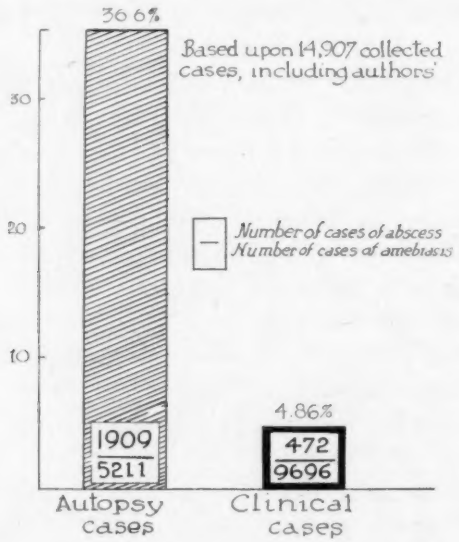
parts of the country and found an incidence of 11.6 per cent in 49,336 individuals examined. Moreover, it would seem that the incidence of infection is increasing. Thus, in a collected series of 19,882 individuals examined before 1930 there was a positive incidence of 10.3 per cent,[409] whereas in a similarly collected group of 28,634 individuals examined since 1930 the incidence was 12.8 per cent.[410] However, as recently emphasized by Faust[118] such surveys are "too few and too fragmentary to provide a complete demographic picture of the infection. For many areas no surveys have been undertaken; for many others the data are based on unrepresentative groups of the population or too few persons have been examined to provide significant statistics. Moreover, most surveys have employed a single technique on a single stool specimen; hence the positive cases reported constitute only a fraction of the true incidence in the particular area." Accordingly, it is his authoritative opinion that, "In the population of the United States an average amebiasis incidence as high as 20 per cent may be reached, rather than the accepted figure of 5 to 10 per cent."

Thus, it would seem that Craig's estimate that between six million and twelve million people in this country are infected with this parasite is too conservative and that a figure of twenty to twenty-five million would be more accurate. The surgical significance of this appallingly high incidence lies in the potential development of hepatic infections. In a previous publication[287] it was shown that approximately 4 to 5 per cent of individuals with intestinal amebiasis develop hepatic complications. Accordingly, on the basis that twenty million people in this country are infected with *E. histolytica*, the potential number of hepatic complications is approximately one million. Such an astounding figure emphasizes with striking clarity the full significance of this important complication.

It is obviously difficult to determine accurately the relative occurrence of complicating amebic hepatitis and hepatic abscess in intestinal amebiasis. The reported statistics vary considerably and depend upon a number of factors. Thus, statistical analyses based upon post-mortem cases will reveal a much higher incidence of hepatic abscess than those based upon clinically observed infections. Obviously, the former cases include patients with more severe amebic infections who are more likely to have complicating liver abscess which is often the cause of death. Moreover, autopsy studies permit more accurate determination of extra-intestinal amebic involvement. In a collected series of 5211 fatal cases of amebiasis,[411] 36.6 per cent were found to have hepatic abscess (Graph II). The lowest incidence in this group was 7.6 per cent[58] and the highest was 84.4 per cent.[349]

As previously stated, the incidence of hepatic abscess in all cases of intestinal amebiasis varies according to different reports and seems to depend upon whether the cases were ambulatory or not. Thus, Futcher[132] reported 27 cases (22.6 per cent) of hepatic abscess in 119 cases of intestinal amebiasis at the Johns Hopkins Hospital. Buchanan,[35]

on the other hand, found that in India the ratio of hepatic abscess to intestinal amebiasis was 1 to 628 in the natives and 1 to 18 in the Europeans. In Peiping, Tao[365] observed an incidence of 1.8 per cent in 1,000 cases of positive amebic infections. In a collected series of 9,696 cases of clinical amebiasis, including the authors', there were 472 cases of amebic abscess of the liver, an incidence of 4.86 per cent[412] (Graph II). In the Charity Hospital group of our series there were 160 cases of amebic hepatic abscess among 1333 cases of amebic dysentery, an incidence of 17.4 per cent. There has been a curious change in the incidence during the fourteen-year period in this institution. Thus, during the six-year period, 1928 to 1933 inclusive, there were 59 (or 15.2 per cent) cases of amebic hepatic abscess among 388 cases of intestinal amebiasis.[277] During the four-year period, 1934 to 1937 inclusive, these respective figures were 59 (or 20.4 per cent) and 288.[287] More recently during the four-year period, 1938 to 1941 inclusive, there



Graph II.—Relative incidence of amebic hepatic abscess in fatal and clinical amebiasis.

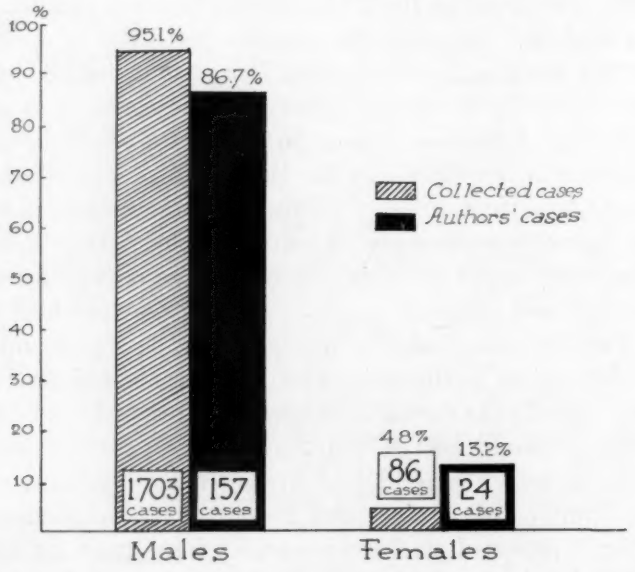
were only 42 (or 6.4 per cent) cases of amebic hepatic abscess in 657 cases of intestinal amebiasis.[285] Thus, it would seem that the incidence of amebiasis has continued to increase but the incidence of complicating hepatic abscess has been decreasing during the last four years although it was increasing up to that time. This would suggest that intestinal amebiasis is being recognized earlier and treated more effectively in recent years. However, as emphasized by Craig,[85] many cases remain undiagnosed especially in the temperate climates where amebiasis is still considered a tropical disease by too many physicians. This author[85] has on numerous occasions found an amebic hepatic abscess at autopsy that was entirely unsuspected before death.

The incidence of amebic hepatitis and hepatic abscess in hospital admissions also varies considerably in different localities and in many in-

stances does not conform to the incidence of amebiasis in the same locality. At the Charity Hospital in New Orleans, during the fourteen-year period, 1928 to 1941 inclusive, there were 784,622 total admissions, among which there were 160 patients with amebic abscesses and 101 with pyogenic abscesses with respective incidences of 0.020 and 0.0128 per cent of the total admissions. During the same period there were 2,538 patients diagnosed as having liver disease, of which 160 (or 6.3 per cent) had amebic hepatic abscess and 101 (or 3.9 per cent) had pyogenic abscesses. In 3,115 hospital surgical patients, Eolian[112] found amebic liver abscess to be present in 0.28 per cent. In Ceylon, Wijerama[394] found an incidence of 1.2 per cent among 4,070 hospital admissions. In South Carolina, Young and Bristow[404] report an incidence of 0.07 per cent in 34,994 total hospital admissions. As commented upon previously,[287] the unusually low incidence of 0.000017 per cent reported by Goldburgh,[141] based upon 120,000 admissions at the Jefferson Hospital and 232,000 admissions at the Philadelphia General Hospital, is rather difficult to explain. Whereas the relative incidence of amebic abscess is considerably greater in the Charity Hospital series (0.034 per cent) than in the Philadelphia group (0.000017 per cent) it is our opinion that this marked difference cannot be explained solely by the slightly higher incidence of amebiasis in the South which according to Craig[85] is only about three times greater. Reports on the incidence of amebiasis in the two regions convincingly demonstrate this fact. Wenrich, Stabler, and Arnett[390] found an incidence of 4.1 per cent of amebic infestation in routine stool examinations on 1,070 college freshmen at the University of Pennsylvania. Similar studies made by Faust and Headler[119] on 4,270 white clinic patients in New Orleans showed an incidence of 8.3 per cent. While the former incidence appears to be one-half as great as the latter it should be realized that college freshmen would be expected to be in better general health than clinic patients. In the authoritative opinions of Craig[72] and Faust[118] both incidences would be much higher if repeated stool examinations were made on each individual. As previously emphasized,[277, 278, 282-284] the relative frequency of amebiasis in the temperate climates is not thoroughly appreciated and consequently the possibility of amebic hepatic abscess is likely not to be considered. In this connection the surprisingly low incidence of amebic hepatic abscess to all liver abscesses recently reported at the Mayo Clinic is of further interest.[34, 166] Only 18 (or 14 per cent) of 125 surgical cases of liver abscess were attributable to ameba,[166] which is in striking contrast with the incidence of 63 per cent amebic hepatic abscess in our series of 287 liver abscesses (Graph I). Surveys made in both areas demonstrate clearly that these contrasting incidences (14 per cent at the Mayo Clinic and 63 per cent in the New Orleans series) cannot be explained solely by the respective incidences of amebiasis in the two regions. Thus, in a total number of 7,302 patients at the Mayo Clinic in which stool examinations were made *E. histolytica* was found in 1,275 (or 17.4 per cent),[138, 228, 338, 347] whereas similar studies on 4,270

white patients in New Orleans showed the incidence to be 8.3 per cent.[119] Faust[117] was also struck by "unexplained discrepancies in different population groups in the same locality." Referring to the incidence of amebiasis according to various surveys he states that, "Clinic patients in Philadelphia have been reported to have an incidence of only 1.1 per cent and college students in the same city 4.1 per cent, food handlers in San Francisco have been found to have only 3.0 per cent infection but University of California students, 53.0 per cent."

The sex factor apparently plays a definite role in the development of amebic hepatitis and hepatic abscess but its exact significance is not clearly understood. Its etiologic importance, however, is demonstrated by the fact that in a series of 1789 cases collected from the literature,[413] 1703 (or 95.1 per cent) were males. In our series of 181 cases there were 157 (or 86.7 per cent) males (Graph III). Rolleston and McNee[330] have attempted to explain this curious susceptibility in the male by the

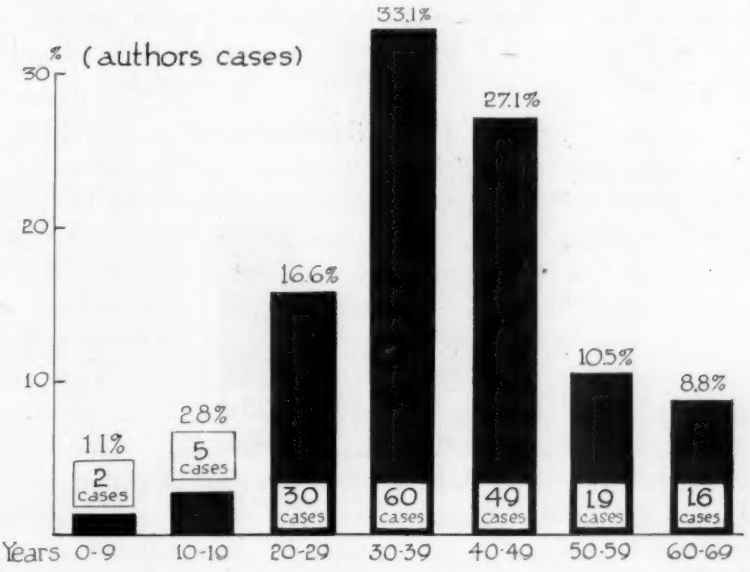


Graph III.—Sex incidence in amebic hepatic abscess based upon 1789 collected cases and 181 cases of the authors.

greater likelihood of trauma and the greater incidence of alcoholism which predispose to hepatitis in this sex. As previously stated, however, a more probable explanation of the preponderance of the male sex in amebic hepatic abscess is the predominant occurrence of intestinal amebiasis in the male. This is demonstrated by Manson-Bahr's[237] recent report of 535 cases of amebic dysentery in which the incidence of males was 83.9 per cent. However, the much higher incidence of intestinal amebiasis in males is yet to be satisfactorily explained.

Amebic hepatitis or hepatic abscess occurs principally during adult life or in the most active period and few cases are observed in individuals less than 20 or greater than 50 years of age. Of almost 400 cases

analyzed by Rogers and Megaw[329] 70 per cent occurred in the third and fourth decades. Ludlow,[218] Craig,[85] and Spittel[353] have reported similar incidences. Palazuelos and Lerner,[292] in an analysis of 74 cases, found that 35.6 per cent occurred in the third decade, 31.5 per cent in the fourth, and 17.8 per cent in the fifth. Whereas its occurrence is rare in children, it has been observed even in infants. In 1824, Brown,[33] although not cognizant of the etiology, observed a case in a 1-year-old negro girl who had a liver abscess following dysentery. Niblock[268] reported a case in a Hindu boy 11 months of age, and Leroy des Barres[209] recorded a case in an eight-month-old infant. Amebic dysentery also occurs rarely in children but as stated by Craig,[85] this is "not believed to be due to any inherent insusceptibility to the infection but to a lesser chance of contracting the infection." In our series of 181 cases the youngest patient was 6 years old, the oldest was 70, and the average age was about 40. The greatest age incidence according to decades was in the fourth and fifth, over 60 per cent of the cases occurring between the ages of 30 and 50 years and almost nine-tenths of the cases occurring between the ages of 20 and 60 years (Graph IV). Thus, our patients

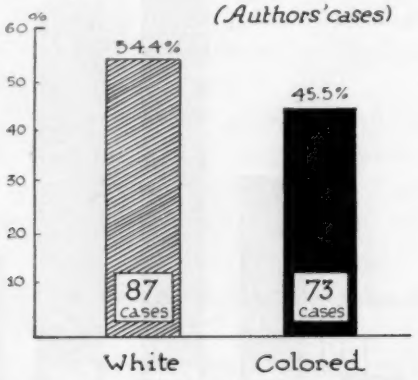


Graph IV.—Age incidence in amebic hepatic abscess according to decades in 181 cases of the authors.

are approximately a decade older than the tropical ones. As previously stated, this is probably due to the greater span of life in the tropics than in the temperate zones.

Whereas all races are apparently susceptible to infection with *E. histolytica* it is the consensus that in the tropics the natives suffer less with clinical manifestations, especially amebic dysentery, than white people. Moreover, a number of observers in the tropics have expressed the opinion that Europeans are more susceptible to the development

of amebic hepatic abscess than natives. Of 568 cases analyzed by Buchanan,[35] 75.8 per cent were white patients and 24.1 per cent natives. Somewhat similar observations were made by Ludlow[218] in Korea, and Herrick[163] in the Canal Zone. On the other hand, in a series of 150 cases reviewed by Huard and Meyer-May,[174] 66 (or 44.4 per cent) were among the white inhabitants and 84 (55.5 per cent) among the natives in Tonkin. Craig[85] believes that the comparative mildness of amebic symptoms among natives in the tropics is "largely due to a partial immunity to the effects of the parasite acquired by constant infection since childhood." In our series of 182 cases, 108 were white and 74 were colored patients. However, only the Charity Hospital group of 160 patients in this series can be considered because colored patients are not admitted to the Touro Infirmary. In this series of 160 cases there were 87 (or 54.4 per cent) white and 73 (45.5 per cent) colored patients, a distribution commensurable with the general admissions to the hospital of the two races (Graph V). As previously stated, the relatively high incidence of colored patients in this group as compared to other reported series may be accounted for, probably, by the fact that only one other institution in New Orleans admits negro patients, and possibly by the fact that white patients are more likely to consider and attempt to obtain antiamebic therapy before admission to the hospital.



Graph V.—Race incidence of amebic hepatic abscess in 160 cases of the authors.

A number of other factors such as alcoholism, traumatism, exposure, improper diet, and lowered resistance have been considered to have some predisposing influence upon the development of amebic hepatitis and hepatic abscess. Of these, excessive indulgence in alcohol is believed by most authorities to be the most important. In fact some have cited the more abstemious habits of females as a significant factor in their comparative freedom from this complication. Rolleston and McNee[330] believe that even the moderate use of alcohol predisposes to amebic hepatitis, as demonstrated by the increased incidence of this complication in natives who are not total abstainers. A number of observers have directed attention to the relatively high incidence of alcoholism in their

studies of the subject. A positive history of alcoholism was obtained by Waring[386] in 67.5 per cent of 40 cases, by Rogers[320] in 54.5 per cent of 44 cases, by Megaw[242] in 70 per cent of 170 cases, and by Chen and his associates[55] in 67.7 per cent of 31 cases. On the other hand Eolian[112] is of the opinion that alcoholism has little or no predisposing influence because the incidence of amebic hepatic abscess is no greater among the natives of Armenia whose habits are far from abstemious in this regard than among the Europeans. This is supported further by the relatively low incidence of alcoholism found in the investigations of other observers. Thus, a positive history of alcoholism was obtained by Peiris[302] in 24 per cent of 28 cases, and by Jayasuriya[188] in only 18 per cent of 73 cases. Unfortunately, the significance of the alcoholic factor cannot be ascertained in our series because in only 10 cases was any statement made concerning its consumption. Of this number 3 gave a positive history and 7 were abstainers.

The significance of seasonal influence upon the development of amebic hepatic abscess is questionable. In an analysis of 236 cases according to the four seasons, Rogers[320] found the incidence almost equal. Rolleston and McNee,[330] however, have expressed the opinion that sudden variations in temperatures are important factors, and Schrumpf-Pierron[340] stated that the sudden occurrence of hot winds in Egypt was the most important cause of recurrence of amebic hepatitis. Whereas climatic factors cannot be considered definitely influential in the development of amebic hepatic abscess, a more definite relationship seems to exist regarding the incidence of amebic dysentery. According to Craig,[85] amebic dysentery occurs more frequently in hot, moist climates and is due probably to the increased possibility of transmission and to the depressing effect upon the resistance of the host.

Pathogenesis.—It has been clearly established by clinical as well as experimental investigations that amebic hepatitis is the result of invasion of the liver by the ameba. The three possible routes by which amebae may gain access to the liver are (1) by direct extension through the bowel wall, peritoneal cavity, and the capsule of the liver; (2) by the lymphatic route; and (3) through the portal vein. Councilman and Lafleur[70] originally contended that amebae "reach the liver by another route than through the blood and lymphatic vessels," that is, "by means of the abdominal cavity"; this was based upon their observations that the most frequent sites of these hepatic abscesses were in the periphery, either on the diaphragmatic or colonic surfaces of the right lobe, and the presence in one case of an associated amebic peritonitis in the right abdominal quadrant. The presence of amebae in the peritoneal exudate and in abscess beneath the right rectus muscle lends credence to this theory.[362] Extension through the lymphatics is based upon the finding of amebae in lymphatic vessels of the colon.[70] However, this mode of transmission is obviously rare, and is probably never operative.

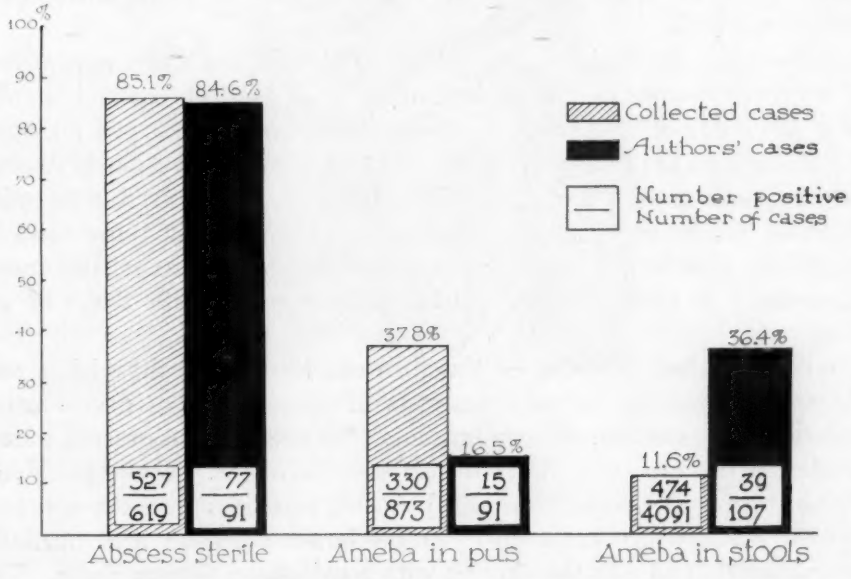
That amebae reach the liver from the primary focus in the intestine through the portal vein is the consensus of most authorities. Amebae are frequently observed in the capillaries and vessels of the intestinal submucosa and in the portal tributaries. According to Rogers[325] if "amebae happen to reach some part of the liver in such numbers as to cause clotting of several contiguous small veins so as to interfere with the blood supply sufficiently to produce a small focal necrosis with consequent softening of the walls of the veins allowing escape of the amebae into the soft liver tissue, the commencement of an abscess results." Once this process begins, further spread of the organisms occurs along the open veins with further destruction of the liver parenchyma and extension of the cavity in concentric circles until a fibrous capsule surrounding the abscess develops.

In the development of amebic hepatitis and hepatic abscess the two factors which play prominent roles are: (1) the production by the amebae of intrahepatic portal thrombosis and infarction, and (2) the cytolytic activity of the ameba. That amebae lodge in the smaller portal radicles producing thrombosis with typical infarction and consequent focal necrosis has been convincingly demonstrated by experimental and clinical investigations.[293, 314] These appear characteristically in the portal triads and extend peripherally towards the capsule, thus paving the way for the cytolytic activity of the amebae to produce lysis and destruction of the involved liver parenchyma. In one of the autopsy cases studied by Palmer,[293] amebae were found in a thrombosed branch of the portal vein in the liver. According to Craig,[85] in the earliest stage of abscess formation "there is an area of capillary congestion surrounding an area composed of cytolyzed tissue cells in which may be seen red blood corpuscles, degenerated liver cells, a few leucocytes, connective tissue cells, and granular debris, with now and then a trophozoite of *E. histolytica* lying in a zone of completely cytolyzed material." Undoubtedly, in many instances this early process of amebic hepatitis does not progress further but heals by connective tissue replacement. That this is not an infrequent occurrence in amebiasis is clearly shown by the fact that sections of liver in cases of active intestinal amebiasis reveal generalized increase in portal connective tissue and focal scar tissue residues of healed small amebic abscesses.

According to this concept it becomes obvious that in the early phase of an amebic hepatitis a balance exists between regression toward healing by scar tissue replacement and progression towards suppuration and abscess formation. Probably the scale is upset by certain predisposing factors such as the relative resistance of the host and virulence and number of the organisms, the presence of pathogenic bacteria, and possibly alcohol, trauma, and other detrimental agencies, resulting in true abscess formation.

The amebae are found characteristically in the zone of necrotic tissue adjacent to the outer dense fibrotic abscess wall. They can be demon-

strated with greatest frequency in the earlier stages of amebic hepatitis or in the marked necrotic tissue of early abscesses and are rarely found in the older abscesses with thick fibrotic capsules. Probably this accounts for the fact that amebae are so difficult to find in the contents of large amebic abscesses, especially when first opened, although several days later they may be found in the "pus."[190] According to MacCallum[222] this may be explained on the basis that amebae require oxygen, and after the abscess has been opened and exposed to the air amebae may readily appear in the draining material. There is considerable discrepancy among different observers concerning the incidence of amebae in the abscess contents. Whereas Rogers,[325] Futcher,[132] and Chen and co-workers[55] were able to demonstrate amebae in the contents of hepatic abscesses in 96.2 per cent, 99.1 per cent, and 65 per cent of their respective series, Okinschewitsch,[289] Bressot,[30] and Huard and Meyer-May,[174] found this incidence to be 12 per cent, 11.9 per cent, and 7.4 per cent respectively in their series of cases. In a series of 873 cases collected from the literature, amebae were demonstrable in the abscess contents in 330 (or 37.8 per cent)[414] (Graph VI). In our



Graph VI.—Respective incidences of sterile abscesses, ameba in pus, and ameba in stools in collected and authors' cases of amebic hepatic abscess.

series of 91 cases, in which the results of this examination were stated, there were only 15 (or 16.5 per cent) with positive findings (Graph VI). The unusually high incidence reported by Rogers,[325] Futcher,[132] and Chen and his associates[55] may be explained by the fact that scraping of the abscess wall was generally performed. In our cases this was rarely done.

Previously the role of pathogenic bacteria in the production of amebic hepatic abscess was a subject of considerable discussion. Whereas pyo-

genic organisms undoubtedly produce hepatic abscesses, in cases of amebic abscess in which they are demonstrable they are probably secondary invaders and usually there is a change in character of the abscess contents. As has been previously emphasized, the fact remains that true amebic hepatic abscesses are characteristically bacteriologically sterile. Relatively large series of cases have been studied by Manson-Bahr,[234] Futcher,[132] and Rogers,[325] who found the "pus" sterile in 91.1 per cent, 86.6 per cent, and 86.2 per cent respectively. In a collected series of 619 cases 527 (or 85.1 per cent) were found to be sterile[415] (Graph VI). An almost similar incidence (84.6 per cent) was found in our series of 91 cases (Graph VI). As previously emphasized,[277-279, 282-285, 287] this is an extremely important fact the significance of which will be better appreciated in the discussion of therapy. The pyogenic organisms most commonly found in secondarily infected amebic hepatic abscesses are streptococci and staphylococci. However, occasionally other forms are observed. Enterococci, *Bacillus coli,* and pneumococci have been reported by Huard and Mayer-May.[174] Of the 14 cases in our series in which secondary infection was present, staphylococci were demonstrable in 8, streptococci in 4, the combination of these two in 1, and *B. coli* in 1.

Pathology.—There is considerable variation in the gross appearance of the liver in amebic abscess depending upon the location and the degree and stage of involvement. Usually the liver is enlarged although if the abscesses are small and deeply situated it may have a fairly normal external appearance. On the other hand localized peritonitis with fibrinous exudation is usually present on the surface in those cases in which the abscess lies near the capsule. Adhesions to the diaphragm are present in those peripherally located abscesses in the dome of the liver.

When the liver is sectioned the abscesses become readily visible and the surrounding parenchyma presents evidence of fatty degeneration and venous congestion. Depending upon the stage of the process macroscopically the abscesses vary in size and character. Upon this basis Councilman and Lefleur[70] classified amebic abscesses into three types: (1) the small, which are acute; (2) the larger abscesses with partially fibrous walls; and (3) the chronic with hard, dense fibrous shells. The earliest visible stage of abscess formation appears as a minute grayish-brown area having a moth-eaten appearance and, according to Craig,[85] represents necrosis of cytolysis of tissue produced by the ameba. From this stage abscesses may be observed ranging in size from a few millimeters in diameter to 15 or 20 cm. Occasionally the abscess actually occupies almost the entire lobe of the liver.

Whereas the contents of the abscess have a characteristic appearance, there may be some variation depending upon the stage and nature of the infection. Thus, in the earlier stages of the nonsecondarily infected amebic abscesses the material has a viscid, glary semitransparent appear-

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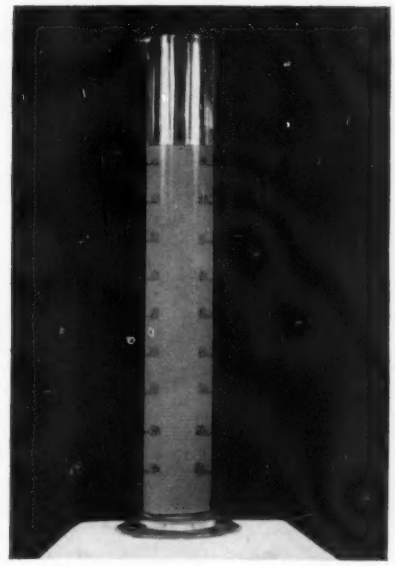


Fig. 1.—Colored photograph showing characteristic chocolate-sauce pus obtained from amebic abscess of liver (Case 3).

ance. Later the contents become less viscid and due to the mixture of blood assume yellowish-red or chocolate-brown color (Fig. 1). This characteristic appearance of the material contained in the abscess has been variously described as resembling "liver scrapings" (raclure de foie),[127] "crushed strawberries" (fraise écrasée),[45] "wine dregs" (lie de vin),[206] anchovy sauce, and "chocolate sauce" which in our opinion[277] is the most descriptive (Fig. 1). According to Costantini[68] and Manson-Bahr[234] this material is so characteristic of an amebic hepatic abscess that its presence justified a positive diagnosis even though amebae are not demonstrable. Once the abscess becomes secondarily infected the contents become more purulent and develop a greenish or grayish-yellow creamy character. However, it should be realized that the contents of a pure amebic abscess do not consist of pus but a mixture of blood, cytolyzed liver tissue, and small solid particles of liver parenchyma which have resisted destruction.

The stage of the lesion also determines the character of the abscess wall. Thus, in the earlier stages of abscess formation the wall may be scarcely visible, whereas in the later stages a dense well-defined fibrous tissue capsule of varying thickness is conspicuously present. According to Craig[85] this typical fibrous wall is "due to the fact that the connective tissue of the liver offers a marked resistance to cytolysis and that the invasion of tissue of this parasite stimulates connective tissue formation." The importance of this limiting fibrous membrane is emphasized by Rogers[325] who believes that once it has formed, further destruction of liver tissue occurs only after secondary infection develops. In medium-sized abscesses the inner aspect of the fibrous wall has a typical shaggy appearance and is covered with shreds of necrotic tissue. This is due to the connective tissue framework of the liver parenchyma which resists the cytolytic activity of the ameba. Cases in which the bands or "shreds of partly cytolyzed connective tissue reach entirely across the abscess cavity" have been described by Craig.[85] The internal surface of the fibrous wall has a smoother appearance in older chronic abscesses.

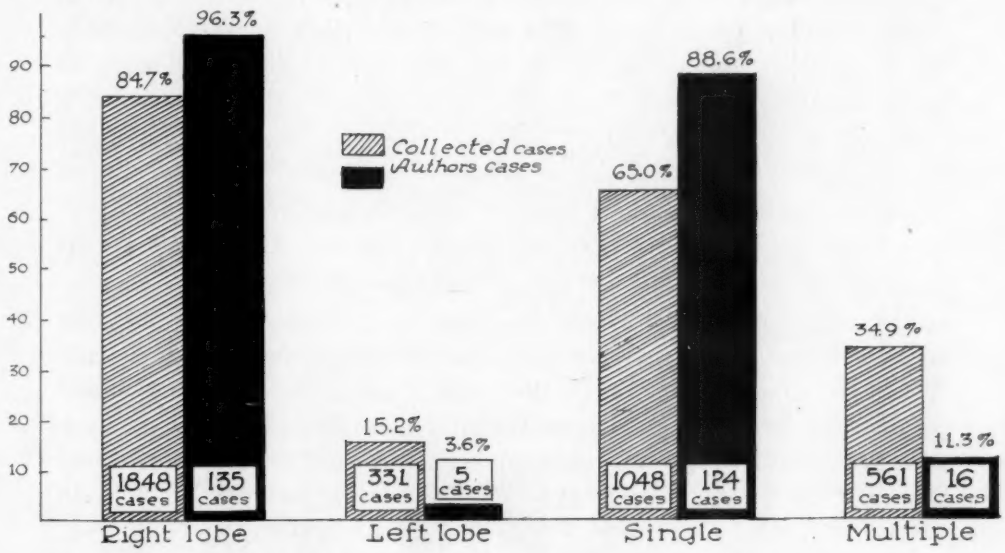
The microscopic appearance of the abscess also varies according to the stage of the process. The lesion is essentially one of the colliquative necrosis and liver parenchymal disintegration with characteristic absence of leucocytic infiltration and inflammatory reaction. In the early stages of amebic hepatitis, section reveals cytolyzed and degenerated liver cells, red blood cells, a few leucocytes and fibroblasts and an occasional ameba surrounded by a zone of capillary congestion. As the lesion advances to true abscess formation a well-defined wall of connective tissue appears surrounding the cavity containing granular necrotic liver tissue, erythrocytes, lymphocytes, and a few polymorphonuclear leucocytes. In the more peripheral areas of the abscess wall, amebae can frequently be observed invading the surrounding liver parenchyma. In the older thick-walled abscesses there is present cytolyzed necrotic tissue contain-

ing fibrin, erythrocytes and monocytes on the inner aspect, and proliferating fibroblasts and lymphocytes near the periphery extending into an area of hyperemia. Calcification of an amebic hepatic abscess is considered most unusual.[180]

Whereas the location and number of amebic hepatic abscesses may be variable, characteristically they are single and occur in the right lobe near the dome of the liver or the inferior surface near the hepatic flexure of the colon. The incidence of right and left lobe involvement and single and multiple abscesses varies according to different authors but depends essentially upon analyses based upon clinical or autopsy cases. Fontan[127] recorded right lobe involvement in 97 per cent of his cases. In their analysis of 150 cases, Huard and Meyer-May[175] found right lobe abscesses in 92 per cent and Moynihan[259] observed an incidence of 71 per cent in this lobe and 16 per cent in the left. Clark,[63] in a study of 95 autopsy cases, found an incidence of 55.7 per cent in the right lobe, 8.4 per cent in the left lobe, 16.8 per cent in the right and left lobes, and 15.7 per cent in all lobes. Left lobe involvement occurs so infrequently that it is considered report-worthy.[149] In a collected series of 2,179 cases the right lobe was involved in 1,848 (or 84.7 per cent) and the left lobe in 331 (or 15.2 per cent)[416] (Graph VII). In our series of 140 cases these respective incidences were 96.3 and 3.6 per cent (Graph VII). Probably the explanation for the higher incidence of right lobe involvement in our series lies in the fact that a large number of autopsy cases are included in the collected series. In previous publications attention was directed to this fact and collected clinical cases revealed a higher incidence of right lobe involvement in the latter and a five times greater incidence of bilateral involvement in the former. Obviously, fatal cases coming to autopsy are more likely to have extensive liver involvement. Moreover, in the clinically observed cases small abscesses may resolve and remain unrecognized under appropriate therapy, whereas thorough post-mortem examination will reveal even these small lesions.

In previous communications we expressed the opinion that predominance of right lobe involvement may be explained possibly on the basis of certain experimental investigations of Sérégé,[341, 342] Glenard,[140] Bartlett, Corper, and Long,[14] and Copher and Dick.[65] These investigators demonstrated the existence of two currents of blood in the portal vein, one from the superior mesenteric vein, which goes to the right lobe, and one from the inferior mesenteric and splenic veins, which goes to the left lobe of the liver. It has been shown by numerous observers that amebic lesions are encountered most frequently in the cecum and ascending colon.[63, 74, 85, 116, 186, 398] In almost two-thirds of 36 cases studied by Rogers[325] the lesions were actually limited to the cecum and ascending colon. In a detailed study of 186 cases, James[186] found that in those cases in which the ulceration was more or less localized the cecum was involved in 87.3 per cent and the ascending colon in 57.1 per cent.

Faust,[116] who recently analyzed 249 autopsy cases from the Gorgas Hospital in Panama and the Charity Hospital in New Orleans, found that the cecum and appendix were the most frequent sites of involvement. Accordingly, the right half of the colon would seem to be the greatest source of amebic infection. On the basis of the two currents of blood in the portal vein this area drains into the right lobe of the liver and consequently there is greater likelihood of amebic localization in this lobe.



Graph VII.—Relative incidence of amebic hepatic abscess according to location and multiplicity of lesions in collected and authors' cases.

Whereas clinically amebic hepatic abscess has been considered characteristically single rather than multiple, varying incidences have been reported depending largely upon analyses of clinical or autopsy cases. Single abscesses were reported by Davidson[94] in 75 per cent, two abscesses in 11 per cent, and more than two in 14 per cent. In analyses of autopsy cases the respective incidences of multiple abscesses found by Gaide,[134] Craig,[75] Sambuc,[337] and Mondon[255] were 30, 60.8, 64.8 and 66 per cent. Further demonstration of the significance of clinical and post-mortem studies on the incidence of single and multiple abscesses is furnished by the studies of Huard and Meyer-May.[174] Whereas in a series of 150 clinical cases multiple abscesses were found in only 13 (or 8.6 per cent), in a series of 43 autopsy cases multiple abscesses were observed in 31 (or 72 per cent). As previously stated the obvious explanation for such discrepancies lies in the fact that autopsy cases are likely to have more extensive involvement and permit more thorough examination than clinical cases. In a collected series of 1,609 cases, a single abscess was present in 1,048 (or 65 per cent) and multiple abscesses in 561 (or 34.9 per cent) (Graph VII).[417] In our series of 140 cases these respective figures were 124 (or 88.6 per cent) and 16 (or

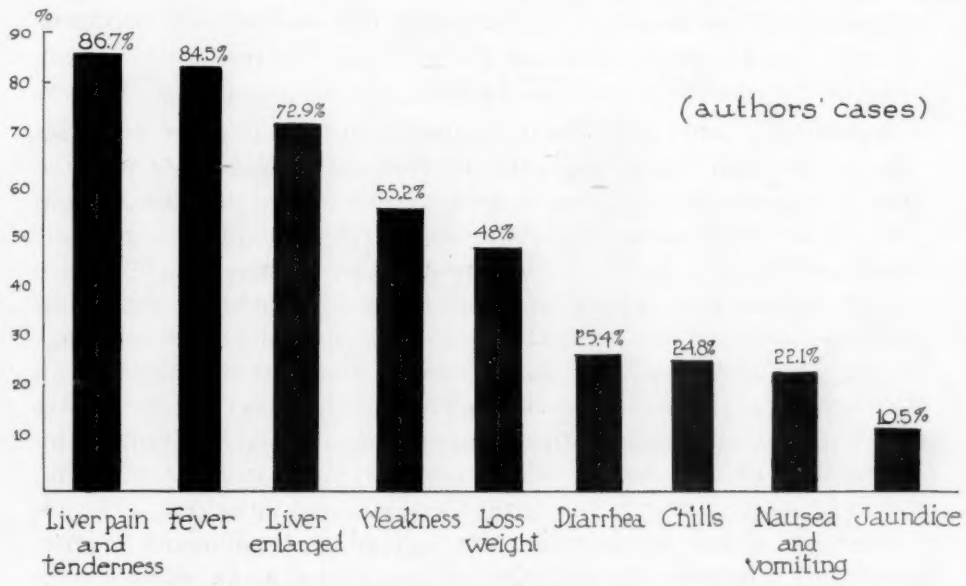
11.3 per cent) (Graph VII). The higher incidence of single abscesses in our series as compared with the collected cases is undoubtedly due to the fact that the great majority of the former were clinical cases, whereas a large proportion of the latter included autopsy cases.

Clinical Manifestations.—The onset of amebic hepatitis or hepatic abscess varies considerably and may be acute, subacute, or insidious depending upon a number of factors such as the virulence of the infection, the resistance of the host, and others previously mentioned in etiology and pathogenesis. Clinical manifestations of this complication also may develop during or immediately following the stage of acute intestinal amebiasis, during active or quiescent periods of chronic intestinal amebiasis, in healthy carriers, or in patients who have never had dysenteric manifestations of intestinal amebiasis. Usually clinical evidence of amebic hepatitis appears early in its development. However, it should be realized that occasionally this may not become apparent until extensive involvement of the liver has occurred.

The period elapsing between the dysenteric manifestations and the onset of liver involvement may vary considerably although it is usually from one to three months.[85] Moreover, during the interim a latent infection of the bowel cannot be definitely excluded. Cases have been recorded in which amebic hepatic abscess developed twenty, thirty, and even forty-three years after the dysenteric manifestations.[194, 217, 231] In some of our cases this period extended from six to eight years.

The importance of recognizing the early development of amebic hepatitis has been emphasized repeatedly.[227-279, 282-285, 287, 329] During this early period or presuppurative stage[329] there is invasion of the liver by amebae but true abscess formation has not yet occurred. The obvious significance of recognizing this period lies in the fact that the institution of appropriate therapy may prevent progression to abscess formation. This is exemplified by Case I reported in this communication. According to Rogers and Megaw[329] the onset during this stage may be considered as acute or chronic. In the former the clinical manifestations are readily evident, quite pronounced, and develop rapidly, whereas in the latter they are much less distinctive and develop more gradually. Determinations of the relative frequency of each type of onset in our series were made by arbitrarily considering cases in which symptoms had clearly developed over a period of three weeks or less, as acute, and those in which the duration was longer, as chronic. Accordingly, in the series of 181 cases, 68 (or 37.6 per cent) were acute and 113 (or 62.3 per cent) were chronic. In the acute group the shortest duration was one day and the average was from ten days to about two weeks. In the chronic group the longest duration was three years and the average from three to six months. Wijerama[394] found in his series of 48 cases that the duration of symptoms was from three days to six months with an average of four weeks.

The clinical manifestations of amebic hepatitis and hepatic abscess may be divided into two groups: (1) systemic, and (2) local. Fever is undoubtedly the most frequent systemic manifestation. Manson-Bahr[234] reported the presence of fever in 85 per cent of a series of 45 cases. In Wijerama's[394] series of 48 cases fever was present in 87 per cent. Palazuelos and Lerner[292] record an incidence of 89 per cent in their series of 74 cases. In our series of 181 cases, fever was the most frequent systemic manifestation, being present in 153 (or 84.5 per cent) cases (Graph VIII). There is some variation in the character and degree of pyrexia depending upon the type of onset and the presence or absence of secondary infection and other complications. Rogers[328] states that in the acute forms fever is high and intermittent or remittent in character, whereas in the chronic types it may even be absent. In our series all the cases in which fever was absent were of the chronic variety.



Graph VIII.—Relative incidence of various clinical manifestations in amebic hepatitis and hepatic abscess based upon analysis of 181 cases of authors.

Sambuc[337] states that in 60 per cent of the cases the temperature is below 38.5° C. According to Chen and co-workers[55] most of their patients had no fever on admission and the average temperature was 37.3° C. Characteristically fever is of a low grade and intermittent in character (Figs. 4, 7, 10, and 17). Definite hyperpyrexia which is septic in type usually indicates secondary infection. The majority of cases in our series were of the former type and only a few fell into the latter category.

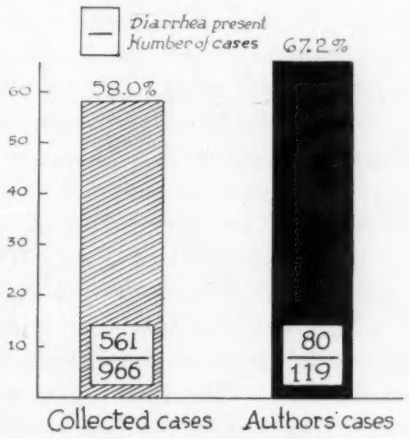
In order of frequency other systemic manifestations are weakness, loss of weight, anorexia, diarrhea, chills and profuse perspiration, nausea and vomiting, sallowness and jaundice (Graph VIII). Obviously the incidence and prominence of these manifestations depend largely upon the extent of hepatic involvement and the development of sec-

ondary infection. Weakness and loss of weight are present in a large proportion of cases and may be pronounced in chronic extensive abscesses. Definite complaints of weakness and loss of weight were found in 55.2 per cent and 48 per cent respectively in our series (Graph VIII). In the more extensive abscesses loss of as much as forty to sixty pounds was recorded. Anorexia, nausea, and vomiting are not infrequently observed, especially in the early stages. In chronic abscesses nausea and vomiting are usually not prominent, and in our series were observed in only 22.1 per cent of the cases (Graph VIII). Chills and profuse perspiration are also not common in the chronic abscesses but are more likely to occur in the acute and subacute forms and those associated with remittent fever. Young[403] reported chills occurring in an incidence of 73.3 per cent in his series of cases but Manson-Bahr[234] found this present in only 4.4 per cent and Peiris[302] stated that profuse sweats were distinctly uncommon. In a previous publication[277] the incidence of chills in a collected series was found to be 24.7 per cent. In our series of 181 cases they were recorded in 24.8 per cent (Graph VII).

According to some observers a peculiar sallowness or dirty yellowish tinge of the skin characteristically develops in amebic abscess of the liver. However, as previously stated, in our experience this is more likely to be encountered in chronic abscess of long duration and extensive involvement and cannot be considered as characteristic of amebic abscess because it is merely an associated manifestation of conditions producing cachexia and emaciation. Actual jaundice occurs relatively infrequently and when deep is indicative of hepatic destruction. In their critical analysis of this subject, Patino Mayer and Pataro[299] state that while jaundice may be due to compression of the bile radicles by enlargement of the abscess, this is relatively rare and the condition should be most commonly interpreted as an amebic hepatosis. The incidence and degree of jaundice vary according to different reports. Rolleston[330] states that it is usually not pronounced and consists merely of a tinging of the sclera; whereas Young[403] found it present in a third of his cases and Palazuelos and Lerner[292] observed a subicteric tinge in 27 per cent of their cases, Ludlow[218] records an incidence of only 3 to 4 per cent, and Peiris[302] and Jayasuriya[188] report an incidence of about 4 and 6 per cent, respectively. Others[250, 251] have reported incidences of about 10 per cent. In our series jaundice occurred in 10.5 per cent and the icterus index varied from the highest figure of 200 to the lowest of 5 with an average of about 38. Palazuelos and Lerner[292] found in their series of 74 cases that the van den Bergh was normal in 50 per cent, slightly increased in 34.6 per cent (6 to 20 mg. per cent), and definitely increased in 15.4 per cent (20 to 60 mg. per cent).

Unfortunately the fallacious impression still exists that diarrhea, whether as an antecedent or an accompanying manifestation, occurs with significant frequency in amebic hepatitis and hepatic abscess. This

may be explained to some extent by the fact that amebiasis and amebic dysentery are generally confused.[85, 282, 283, 287] As previously stated, it should be thoroughly realized that amebic hepatic involvement occurs in a relatively large number of patients who have never had a previous diarrhea. This is a particularly significant fact in the diagnostic consideration of amebic abscess of the liver and we have emphasized this repeatedly.[277-279, 282, 285, 287] An antecedent history of diarrhea was found in about 45 per cent of the series studied by Jayasuriya,[188] Peiris,[302] and Staffieri[354] and in about 60 per cent of those analyzed by Manson-Bahr,[234] Murray,[259a] and Thurston.[373] In a series of 966 cases collected from the literature only 561 (or 58 per cent) or a little more than one-half had a positive history of antecedent diarrhea[418] (Graph IX). In our series this incidence was 67.2 per cent and the diarrhea was a symptom at the time of admission to the hospital in only 25.4 per cent (Graph IX). Thus, in from one-third to almost one-half the



Graph IX.—Incidence of history of diarrhea in amebic hepatic abscess.

cases history of an antecedent diarrhea will not be obtained. This is explained on certain anatomicopathologic features of amebic infections. On the basis of clinical[13, 84, 103, 262, 371, 398] as well as experimental[87, 162, 196] observations it has been clearly established that amebic infection of the large bowel may exist in the absence of dysenteric manifestations. Such manifestations occur most commonly in rectal amebiasis but as stated above it has been shown by numerous observers that amebic lesions are encountered most frequently in the cecum and ascending colon. Thus, the probable explanation for the relatively high incidence of amebic hepatitis in the absence of an antecedent diarrhea is based, as previously presented by us,[95, 278, 287] on the frequency of localization of amebic infections to the right half of the colon and the respective differences in function of the right and left halves of the colon. Relatively slight infections limited to the sigmoid and rectum produce irritation and excessive secretions of fluids with consequent dysenteric manifestations,

whereas similar lesions limited to the cecum and ascending colon do not cause diarrhea because the fluid is absorbed in its passage through the uninvolved and normally functioning left side of the colon. In complete accord with this explanation, Solier and Dejou[350] recently reported a case in which autopsy studies were made and which exemplified this concept.

Probably the earliest and most constantly encountered local manifestations of amebic hepatitis are pain and tenderness in the region of the liver. The frequency of localized pain and tenderness is revealed by the fact that various observers have reported its incidence in from 75 to almost 100 per cent.[419] In our series these were the most constant manifestations having an incidence of 86.7 per cent (Graph VIII). Varying in character from a dull aching discomfort to a severe sharp pain it is usually located directly over the liver, although it may be most pronounced immediately below the right anterior costal margin, in the epigastrium, about the ninth interspace in the axillary line, or posteriorly over the twelfth rib. Not infrequently radiation to the shoulder, usually the right, is a prominent complaint and may be explained on the basis of diaphragmatic irritation. Its significance has been emphasized by Manson-Bahr[234] who found it present in 44.4 per cent on the right and in 4.4 per cent on the left. In the latter, abscesses of the left lobe were present. On the other hand shoulder pain was present in only about one-sixth of Manson's[232] series, one-fifth of Jayasuriya's[188] series, and about one-twentieth of Huard and Meyer-May's series.[174] Similarly, in our cases shoulder pain was recorded in 16.6 per cent. Ludlow[218] has described a sign which he considers of diagnostic significance and consists of a deep-seated pain produced by a sudden thrust of the end of the finger on the liver. The most common point at which this can be elicited is about two inches below the right costal margin. Boccia[24] has observed subxiphoid tenderness (Castellani's sign) as a significant manifestation in amebic hepatitis.

The next most constant local manifestation of amebic hepatitis and hepatic abscess is enlargement of the liver. Whereas, it may not be obvious on physical examination, most experienced observers agree that a varying degree of hepatomegaly is almost invariably present. Different observers have reported incidence of hepatomegaly varying from 64 to 100 per cent.[234, 292, 366, 394, 403] In our series of 181 cases, the liver was clinically enlarged in 72.9 per cent (Graph VIII). Manifestations of liver enlargement are sometimes apparent by widening of the lower right intercostal spaces with some restriction of respiratory movement on this side and possibly some dilatation of the superficial veins. Usually the liver margin can be palpated below the right costal arch anteriorly and on percussion liver dullness will be found to extend higher than normal, especially in the mid- or posterior axillary line. Frequently tenderness and some rigidity of the abdominal muscles in the upper right quadrant can be elicited. Occasionally there may be observed in

this area a distinct localized bulging with redness and edema of the skin indicating involvement of the abdominal parietes.[351] Associated diaphragmatic pleurisy and basal lung changes on the right side are not uncommon and are due not only to compression of the lower portion of the right lung but also to contiguous inflammatory involvement. Such disturbances are manifested by localized pain especially on deep inspiration, a hacking nonproductive cough, dullness, diminished breath sounds, crepitant râles, and a friction rub. In some there may be signs of fluid in the pleural cavity. Such signs occur with varying frequency and obviously depend upon the extent of hepatic involvement. Wijerama[394] reported such findings in a third of the cases and Jayasuriya[188] in slightly over one-half.

Laboratory Findings.—The most informative laboratory procedures in amebic hepatitis and hepatic abscess are certain blood studies, stool examination, and roentgenography. Of the blood studies the leucocyte count is probably the most significant. Various observers[95, 238, 277-279, 282-287, 328] have directed attention to the moderate leucocytosis in amebic hepatitis and hepatic abscess as contrasted with the pronounced leucocytosis occurring in the pyogenic forms. Moreover, in the former, characteristically there is not a concomitant increase in polymorphonuclear leucocytes. In their group of cases, Manson-Bahr and Willoughby[238] found that the highest leucocyte count was 25,000, the lowest 7,500, and the average 15,000 with no eosinophilia. They also observed that the lowest counts were associated with the largest abscess cavities. In their series of 150 cases, Huard and Meyer-May[172, 177] found the leucocyte count to be between 10,000 and 16,000 in one-half of the cases and between 8,000 and 10,000 in the other half. In his study of 73 cases, Jayasuriya[188] found the leucocyte count to vary between 10,000 and 30,000 with an average polymorphonuclear percentage of 69. Wijerama[394] recorded counts between 8,000 and 32,000 with an average of 12,000 and an average polymorphonuclear percentage of 72. These respective figures in the series studied by Palazuelos and Lerner[292] were 2700, 29,000, 12,500, and 74.1 per cent. In our series these findings are summarized in Table I. Accordingly, it may be observed that variations in the leucocyte count apparently depend upon the chronicity of the process. Thus, while the average leucocyte count was 16,460 in the acute forms, it was somewhat less than 13,000 in the chronic type. It may be stated that in general as the lesion becomes more chronic the leucocyte count diminishes. Rogers[327] has expressed the opinion that high leucocytosis indicates multiple abscesses and a bad prognosis. In our experience a pronounced leucocytosis usually indicates secondary bacterial invasion, an observation which Wright[399] has also recently observed. This may be illustrated to some extent by the contrasting leucocyte counts in the amebic and pyogenic hepatic abscesses that we have studied.[286, 287] Thus, the average leucocyte count in acute pyogenic hepatic abscesses was found to be 26,924 whereas in amebic abscesses

TABLE I

BLOOD PICTURE IN AMEBIC HEPATIC ABSCESS*

	ACUTE	CHRONIC	TOTAL
Leucocytes:			
Lowest	7,500	2,000	2,000
Highest	31,500	23,000	31,500
Average	16,460	12,700	14,300
Neutrophiles:			
Lowest	60%	59%	59%
Highest	97%	95%	97%
Average	79%	75%	78%
Hemoglobin:			
Lowest	50%	30%	30%
Highest	90%	90%	90%
Average	72%	60%	66%
Erythrocytes:			
Lowest	2,650,000	1,950,000	1,950,000
Highest	4,975,000	4,800,000	4,975,000
Average	3,872,000	3,490,000	3,670,000

*Based on analysis of authors' cases.

the corresponding figure was 16,460. The eosinophile count in amebic hepatic abscess was not found significant. An associated secondary anemia is present in the majority of cases and is more pronounced in the chronic forms. Thus, the average hemoglobin percentage was 72 in the acute cases and 60 in the chronic, while the average erythrocyte count was 3,872,000 in the former and 3,490,000 in the latter.

In 1927, Craig[78] demonstrated the presence of specific complement-fixing properties for *E. histolytica* in the blood sera of persons harboring this parasite and thus established the basis for the complement fixation test. Subsequent investigators[420] fully confirmed the meritorious investigations of Craig.[79-82, 86-88] The high degree of specificity that has been demonstrated with this test and the results that have been obtained clearly indicate its usefulness as a diagnostic laboratory procedure in questionable cases of amebiasis and especially in amebic hepatitis and hepatic abscess. The technique which is similar to the standard complement fixation test for syphilis with appropriate modifications in the antigen has been described in a number of previous publications.[421] Unfortunately, the difficulty experienced in obtaining a potent antigen has greatly hindered the routine use of this test in the clinical laboratory. Accordingly, as stated by Faust,[117] "Until the preparation of *E. histolytica* antigen is simplified, it cannot become generally available for the clinical laboratory."

Examination of the stools for the presence of amebae is another important laboratory procedure although their incidence varies considerably according to different reports. Thus, Tao[365] records their presence in the stools in 77.7 per cent of his cases, whereas Manson-Bahr[234] found a positive incidence in only 4.4 per cent and Palazuelos and Lerner[292] in only 13.5 per cent. Chen and his associates[55] reported an incidence of 34.1 per cent and Wijerama,[394] 31.2 per cent. In a collected series[422] of 4,091 cases, amebae were reported present in the stools in 474 (or

11.6 per cent) and in our series of 107 cases in which the results of this examination were stated amebae were found in 39 (or 36.4 per cent) (Graph VI). As previously stated this incidence will undoubtedly be greatly influenced by the experience of the examiner, the technique employed, and the repetition of examination in each case.

Roentgenography is undoubtedly one of the most important and dependable diagnostic laboratory procedures in amebic hepatic abscess. Among the early investigators who recognized the significance of radiologic examination in amebic hepatic abscess are Loison,[212] Quadrome,[312] Béclère,[17, 18] and others.[43, 164, 187, 210, 300] Numerous observers have directed attention to the characteristic elevation and immobility of the diaphragm.[99, 205, 295] Accordingly, it is important to perform fluoroscopic examination of the patient in the upright position. Moreover, as emphasized by Pancoast,[295] the presence of lung reaction is of diagnostic significance and when present usually indicates an amebic infection because these abscesses occur most frequently on the convex surface of the liver in close contact with the diaphragm. The inestimable value of certain characteristic roentgenologic changes in amebic hepatic abscess and subdiaphragmatic suppuration has been repeatedly stressed by Granger[144] and by us.[277-287] In uncomplicated abscess of the liver, a distinct bulging of the diaphragm may be observed pointing upward into the lower lung field in both the anteroposterior (Figs. 2, 5, and 8) and lateral roentgenograms (Figs. 3, 6, 9, and 11). The presence of this picture is considered almost pathognomonic. Moreover, it is possible to distinguish subphrenic abscess complicating a liver abscess from that due to other causes. Thus, in the former there occurs characteristically an obliteration of the cardiophrenic angle in the anteroposterior roentgenogram (Figs. 2, 5, and 8), and obliteration of the anterior costophrenic angle in the lateral view (Figs. 3, 6, 9, and 11). On the other hand, in subphrenic abscess due to other causes obliteration of the costophrenic angle is present in the anteroposterior roentgenogram and the posterior costophrenic angle in the lateral view. Although abscesses of the left lobe of the liver occur relatively infrequently their presence has been difficult to demonstrate. For this reason the roentgenologic method described by Miles[254] is of distinct value. He has shown that abscesses in this lobe produce characteristic pressure deformities on the barium-filled stomach. The cardia and duodenal cap are displaced and the lesser curvature assumes a typical crescentic shape.

The inestimable value of roentgenography in the diagnosis of amebic hepatic abscess is clearly demonstrated by the reports of various observers. A positive diagnosis was obtained by Young and Bristow[404] in all of a series of 25 cases. Huard and Meyer-May[174] reported a positive diagnosis in 80 per cent of 70 cases and Palazuelos and Lerner[292] in 69 per cent of 74 cases. In our series, there were 150 cases in which roentgenologic studies were made with positive diagnosis in 132 (or 88 per cent).

Modifications in technique, presumably as aids in the roentgenologic diagnosis of liver abscess, have been suggested by a number of observers. Some have advocated aspiration of pus from the abscess cavity and the introduction of an iodized oil followed by roentgenologic studies.[423] Accordingly, the size, shape, and position of the abscess may be visualized better and its drainage and progress controlled more satisfactorily. In more recent communications a number of authors emphasize the value of this procedure.[424] A slight modification of this technique consists of injecting air in addition to a small amount of lipiodol and taking roentgenograms with the patient in various positions.[41, 105] Chung and his co-workers[60] believe that this permits better delineation of the abscess cavity. They studied 5 cases in this manner over a period of time and interpreted the continued presence of lipiodol in the liver for almost a year as indicating that the abscess had not yet completely healed. Accordingly they state that whereas the patient may appear clinically cured the loss of liver tissue consequent to the abscess is so great that it may require weeks or months to heal completely. Although this may be true, one wonders to what extent the presence of the lipiodol contributed to the prolongation of this period. Under these circumstances lipiodol is injected into a closed space and it is well known that lipiodol injected into a closed space in other parts of the body remains present for long periods of time. Sarmiento[339] has recently voiced his objection to this procedure on the basis that it is usually unnecessary and the possibility of secondary infection may even be dangerous. Whereas under certain circumstances the procedure may be of diagnostic value, in our opinion it should not be employed routinely. Hepatography is still another method advocated and employed by some observers for visualization of the abscess.[36, 315, 401, 402] This is done by the intravenous administration of thorium dioxide and the abscess appears on the roentgenogram as a negative shadow. As previously emphasized, this procedure appears unjustified in view of the present state of insufficient knowledge regarding the end effects of thorium dioxide, particularly in a condition which otherwise can be so readily diagnosed.[277, 278, 287, 331] In 1932, the Council on Pharmacy and Chemistry[372] directed attention to the possible deleterious effects of the intravenous administration of such a radioactive substance as thorium dioxide. Subsequently, the proclivity of this substance to produce damage to tissue was emphasized further by numerous clinical and experimental observations.[107]

Diagnosis.—The diagnosis of amebic hepatitis and hepatic abscess is not difficult if the conditions are kept in mind and the clinical manifestations and laboratory examinations accorded due consideration. An amebic hepatitis should always be considered in a patient presenting a low-grade daily remittent or intermittent fever, pain and tenderness over the liver area, moderate leucocytosis without a concomitant proportionate increase in polymorphonuclear leucocytes, and *E. histolytica* in the stools. Such a clinical picture during or shortly after an attack

of amebic dysentery more strongly indicates the presence of an amebic hepatitis. However, it should be realized that even in the absence of intestinal manifestations the condition should be considered, repeated stool examinations should be done, and every attempt made to confirm or exclude the diagnosis of amebic hepatitis. The significance of early recognition of this condition has been emphasized repeatedly and lies in the fact that the institution of appropriate therapy during this presuppurative stage may prevent progression to abscess formation.[133, 277, 278, 285, 287, 329] This is clearly demonstrated by Case I reported herein.

Whereas there is some variation in the clinical manifestations of amebic hepatic abscess depending upon the chronicity of the process, persistent hepatomegaly, pain and tenderness over the hepatic area with occasional radiation to the shoulder, and a daily remittent or intermittent fever of moderate degree are fairly constant manifestations. The presence of these symptoms and signs should always suggest the possibility of an amebic hepatic abscess. Anorexia, loss of weight and strength, nausea and vomiting, profuse perspiration, and disturbed slumber are less constantly observed, but their presence lends further support to the diagnosis. The presence of an antecedent dysentery is confirmatory evidence but its absence is not refutatory. It will be recalled that from one-third to almost one-half the patients gave no history of a previous dysentery. The diagnosis is supported further by a mild leucocytosis without a disproportionate increase in polymorphonuclear leucocytes. If, in addition to such a clinical picture, the characteristic fluoroscopic and roentgenologic findings previously described are present, the diagnosis of amebic hepatic abscess is justified. The demonstration of active or encysted forms of *E. histolytica* is corroborative evidence but their absence does not exclude the diagnosis.

It must be realized, of course, that whereas these findings justify the diagnosis of amebic hepatic abscess, its establishment depends upon the demonstration of the characteristic chocolate sauce pus (Fig. 1). Herein lies the diagnostic importance of exploratory aspiration. However, the procedure should not be performed without thorough cognizance of its possible dangers. Of these the most important are (1) hemorrhage, and (2) extension of infection. Various investigators have directed attention to the possibility of hemorrhage and have reported cases in which this dangerous complication followed exploratory aspiration of an amebic hepatic abscess.[425] Fatal hemorrhage occurred in over 20 of the reported cases according to Huard and Meyer-May;[174] Hatch[160] and Rogers[326] have emphasized the fact that this danger is greater in the acute stage of hepatitis with pronounced congestion of the liver. Accordingly, it may be almost entirely avoided by the administration of emetine for several days preceding the aspiration and thus controlling the associated hepatitis. As previously emphasized by us[287] extension of infection is another danger which deserves special consideration.

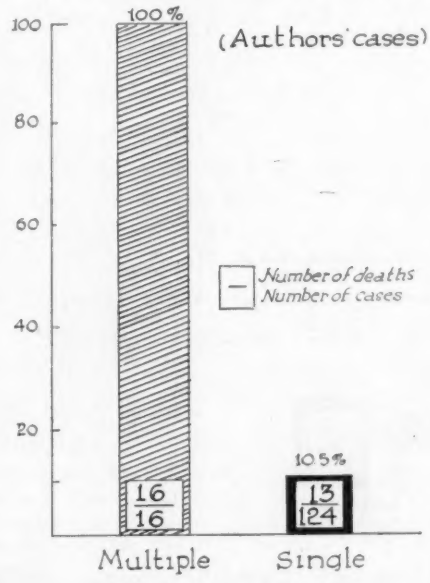
Since it is not always possible to determine clinically whether an amebic hepatic abscess is sterile or contains pyogenic organisms, the latter possibility should always be assumed and the aspiration performed in such a manner that an uninvolved portion of the peritoneum or the pleural cavity is not traversed by the aspirating needle. Obviously this is not always possible but the consideration should be kept in mind during the attempted aspiration. It should be realized, also, that this is not as difficult in the presence of an enlarged liver containing an abscess as under normal conditions, for in the former the anatomic relationships have been changed.

These hazardous possibilities, hemorrhage and extension of infection, may be avoided largely by preaspiration emetine therapy, the type of needle employed, the technique of aspiration, and the performance of the procedure in the operating room under absolutely aseptic precautions. Emetine hydrochloride should be administered for at least two to four days prior to aspiration in one grain (0.06 Gm.) doses daily. By employing a needle not longer than 10 cm. with a calibre not greater than 2 mm. the danger of puncturing a large vessel is minimized.[174, 219, 235] We prefer a short beveled needle or a trocar type with a short, fairly blunt point. The procedure should always be performed in the operating room, first, because aseptic precautions are likely to be greater and second, because if the abscess is found to be secondarily infected open drainage can be done immediately. This latter possibility can be readily determined by an immediate smear of the aspirated pus which will reveal upon microscopic examination the presence of large numbers of bacteria and leucocytes in those cases in which secondary infection is present. Whereas general anesthesia can be employed, local infiltration analgesia using 1 per cent procaine hydrochloride solution is preferable. Nicking the skin at the contemplated site of puncture with a bistoury will facilitate insertion of the needle.

The cutaneous site of puncture and the direction of the introduction of the needle depend largely upon the clinical and radiologic findings. Accordingly, in the presence of localizing signs and pointing of the abscess, the needle should be introduced directly over the mass or at the site of greatest tenderness. However, if no localizing signs are present, the roentgenograms may be of guiding significance. Thus, in a case in which the lateral roentgenogram demonstrates the abscess in the anterior portion of the liver, the needle may be inserted just below the anterior costal margin about 4 to 6 cm. lateral to the midline and directed superiorly and posteriorly (Fig. 22). On the other hand, if the lateral roentgenogram reveals posterior localization of the abscess, the needle should be introduced below the costophrenic angle and directed superiorly and anteriorly (Fig. 23). However, in those cases in which the abscess is located more anteriorly near the dome of the liver, as occurs most frequently, avoidance of the pleural and peritoneal cavities may be accomplished best by inserting the needle in the ninth or tenth

intercostal spaces in the anterior axillary line and directing it superiorly, medially, and slightly posteriorly (Fig. 24). Occasionally it may be necessary to puncture the liver in several different directions before pus is encountered. Accordingly, if multiple punctures are necessary it is extremely important to remove the needle entirely before reintroducing it in a different direction rather than changing its direction while the needle is still at its original site. In this way extensive injury to the friable liver parenchyma may be prevented.

Prognosis: A number of factors influence the prognosis in amebic hepatitis and hepatic abscess. In addition to the relative number and virulence of the parasite and the resistance of the host, the most important factors are: (1) the multiplicity of lesions in the liver; (2) the presence or absence of complications; (3) the presence or absence of secondary infection; and (4) the type of therapy employed.

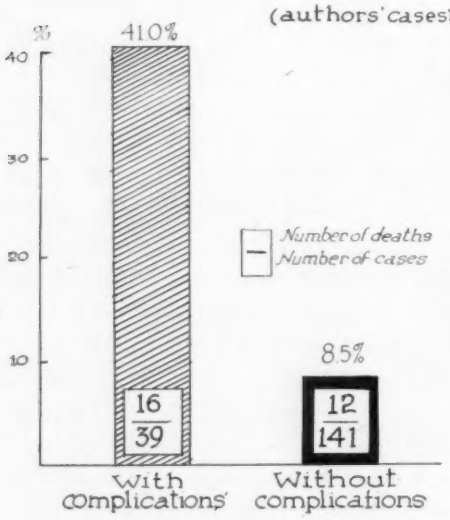


Graph X.—Mortality incidence of amebic hepatic abscess according to multiplicity of lesions in 140 cases of authors.

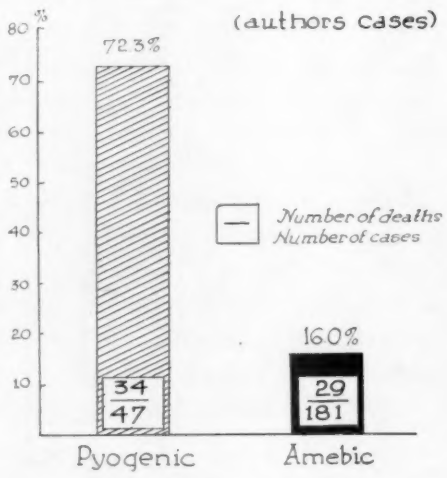
That multiple abscesses increase the gravity of the condition has been shown by a number of observers. Sambuc[337] found that the mortality was 23 per cent in cases with single abscess, 45 per cent in those having two abscesses, 90 per cent with three abscesses, and 100 per cent in patients having more than three abscesses. Of 137 cases with single abscess, analyzed by Huard and Meyer-May,[174] 23 (or 16.7 per cent) died, and in 13 cases with multiple abscesses the mortality was 100 per cent. Of 45 collected cases of multiple abscesses and recurrences Huard[170] found that the mortality was 44.4 per cent. Similar analyses in our series demonstrate further the prognostic significance of multiplicity of lesions. Thus, the mortality in 16 cases with multiple abscess was 100 per cent, whereas in 124 cases with single abscesses it was only 10.5 per

cent (Graph X). Of interest in this connection is the statement of Craig[85] that, "it is doubtful if the mortality of amebic abscess of the liver is ever less than 25 to 30 per cent if multiple abscess cases are included. . . ."

It is also to be expected that the presence of complications would influence materially the prognosis of amebic hepatic abscess. This is clearly demonstrated by the reports of various observers and the results obtained in our series. According to Huard and Meyer-May[174] the mortality in a series of 46 cases with complications was 34.7 per cent, whereas in a group of 104 cases without complications it was 19.2 per cent. This difference is even more pronounced in our series as the mortality in 39 cases with complications was 41 per cent in contrast with 141 cases without complications in which the mortality was 8.5 per cent (Graph XI).



Graph XI.



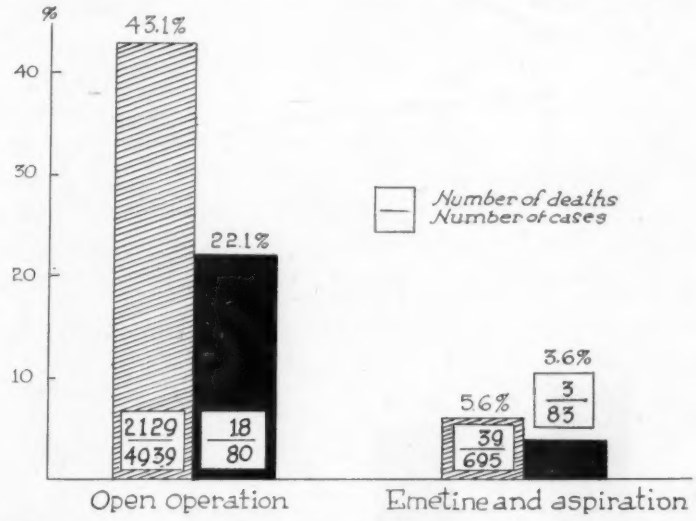
Graph XII.

Graph XI.—Mortality incidence of amebic hepatic abscess according to presence or absence of complications in 180 cases of authors.

Graph XII.—Respective mortality incidences in amebic and pyogenic hepatic abscesses based upon 228 cases of authors.

The fact, demonstrated above, that the majority of amebic hepatic abscesses are sterile is extremely significant in the prognostic as well as the therapeutic consideration of the condition. As emphasized previously, its decisive importance is insufficiently realized. After an amebic hepatic abscess becomes secondarily infected it can no longer be considered an amebic lesion but prognostically and therapeutically must be regarded as a pyogenic process. The invasive pathogenic and toxic characteristics of pyogenic microorganisms differ considerably from the relatively benign and limiting features of the purely amebic lesion of the liver. The contrasting mortality rates in the two conditions emphasize this fact with striking clarity. Thus, in a previously reported

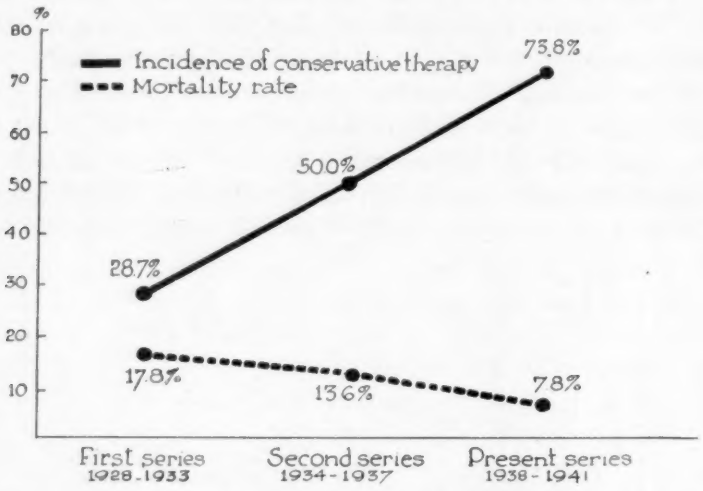
series of 47 cases of pyogenic hepatic abscess the mortality was 72.3 per cent, whereas in this series of 181 cases of amebic hepatic abscess the mortality is 16 per cent (Graph XII). As previously stated, the deleterious effects of secondary infection of a sterile amebic abscess may be better realized if the analogy is made to the similar morbiferous change which occurs in a tuberculous abscess that becomes secondarily infected.[265, 326] It is a well-established fact that the secondary infection of a tuberculous process greatly increases the gravity of the prognosis. For these reasons it is obvious that the avoidance of secondary infection in amebic hepatic abscess is paramount. Accordingly the type of therapy assumes increasing significance. In spite of meticulous care and scrupulous precautions to avoid it, secondary infection invariably follows open drainage of an abscess which is relatively sterile. Only by



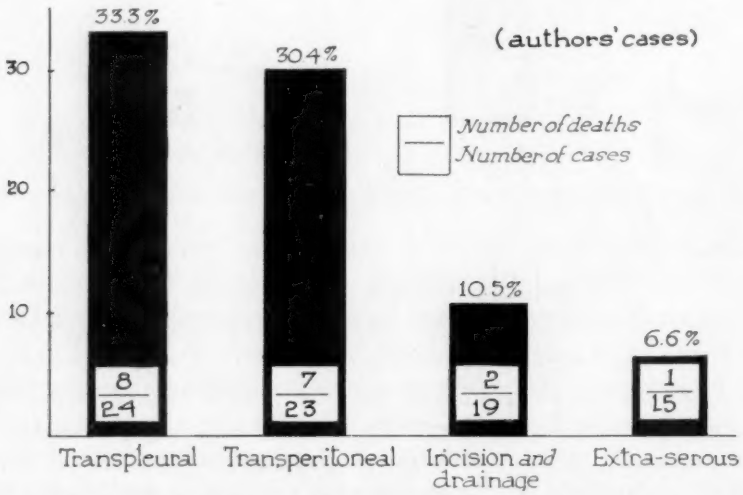
Graph XIII.—Mortality in amebic hepatic abscess according to type of therapy.

closed drainage, i.e., aspiration, is it possible to evacuate the abscess and simultaneously maintain its sterility. The striking contrast in the mortality rates obtained by various investigators who have employed the two methods of therapy irrefutably demonstrates this fact. Approximately 20 years ago, Rogers[326] made the observation that the mortality was decreased from 56.8 per cent in cases having open drainage to 14 per cent in those treated with closed drainage. Similarly, Chatterji[50] was able to reduce the mortality from 26 per cent in 69 cases with open drainage to 1.6 per cent in 186 cases with closed drainage. This is demonstrated more forcefully by the results in a large series of cases collected from various parts of the world. Thus, in a collected series of over 5000 cases the mortality was 43.1 per cent in those treated with open drainage,[426] and 5.6 per cent in those receiving closed drainage[427] (Graph XIII). These corresponding figures in our series were 22.1 per cent and 3.6 per cent (Graph XIII). Of even greater significance in

this connection is the consistent decrease in the total mortality rates in our cases during the three periods studied. This is undoubtedly due in great measure to the increasing employment of closed drainage. Thus, in the first series of 73 cases studied, the incidence of closed drainage was 28.7 per cent and the total mortality was 17.8 per cent; in the second



Graph XIV.—Respective mortality incidences in authors' three series of amebic hepatic abscess as compared to incidence of employing conservative therapy. Graph shows that mortality decreases as incidence of employing conservative therapy increases.



Graph XV.—Relative mortality incidence in amebic hepatic abscess according to type of operation in 81 cases of authors.

series of 66 cases these respective figures were 50 per cent and 13.6 per cent; and in the present series of 42 cases these corresponding incidences were 73.8 per cent and 7.8 per cent (Graph XIV). It may be graphically observed, therefore, that as the incidence of employing conservative therapy increases the mortality decreases (Graph XIV).

The prognosis of amebic hepatic abscess is also influenced by the type of operation employed in those cases in which open drainage is indicated. Since these cases are secondarily infected the contents of the abscess must be considered pyogenic. Accordingly, the institution of that type of drainage which completely avoids the slightest possibility of contamination of the two virgin serous cavities, the pleural and the peritoneal, becomes an absolute desideratum. As we have emphasized in previous communications,[277, 281–287] it is obvious that if an uninvolved serous cavity is in jeopardy of contamination by the type of drainage used the prognosis is much worse, not only regarding subsequent morbidity but also regarding life. The results obtained in our series of cases in which open drainage was used demonstrate these facts with graphic clarity. Thus, the mortality in 24 cases with transpleural drainage was 33.3 per cent and in 23 cases with transperitoneal 30.4 per cent, whereas in 15 cases drained by the extraserous route the mortality was only 6.6 per cent (Graph XV). There were 19 cases drained by simple incision over the abscess with a mortality of 10.5 per cent (Graph XV). Since these abscesses had become attached to the parietes and thus sealed off the serous cavities, drainage in these cases might also be considered extraserous. Accordingly, the total mortality in those having extraserous drainage would be 8.8 per cent contrasted with 31.9 per cent in those drained transserously.

(To be concluded in the April issue. The references will accompany the last section.)

Book Reviews

Surgery of the Heart. By E. S. J. King, M.D., F.R.C.S., Major, A. A. M. C., University of Melbourne. Ed. 1. Pp. 728, illustrations 268. Baltimore, 1941, Williams & Wilkins Company. $13.50.

This monograph, fathered by a surgeon, is in many respects an unusual book. It essays to deal with surgical disorders of the heart from the standpoint of radiologic, clinical and electrocardiographic diagnosis, as well as surgical treatment. That obviously is an ambitious undertaking. Yet, the author has done this difficult task in a surprisingly effective manner.

The title of the book may suggest that the book was intended primarily for the surgeon. Such, however, is not the case, for the treatment of the subject matter from the technical, operative point of view is by no means exhaustive. It is not a book on operative surgery of the heart, though the essential features of operative procedures are described. The book is described best, probably, as a pathologic and clinical treatise on those diseases of the heart in which surgical treatment may play a useful role. A number of unusual conditions, such as tumors of the heart and cysts of the pericardium, are described. Yet the book fails to describe the surgery of patent ductus arteriosus or of peripheral arteriovenous communication which may provoke heart failure.

There is much to commend in the monograph. Those interested in the surgery of the heart will find the book an extremely useful source book.

Textbook of General Surgery. By Warren H. Cole, M.D., F.A.C.S., professor and head of department of surgery, University of Illinois, and Robert Elman, M.D., Washington University, St. Louis. Ed. 3. Pp. 1067, illustrations 558. New York, 1941, D. Appleton-Century Company, Inc. $8.

This general text on surgery has come to occupy an important place amongst textbooks of surgery. In this, the third edition, the authors invited well-known surgical authorities in their respective fields of interest to review the subject matter. Undoubtedly the authors got from these consulting collaborators a number of worthwhile suggestions which have pyramided the value of the text. The monograph embraces the entire province of surgery. The only surgical specialties which receive no notice in the book are those concerned with diseases of the eye, ear, nose, and throat.

The text is well illustrated and appropriate bibliographic references accompany each chapter. The authors, both teachers of surgery, obviously have lent a good deal of thought, time, and effort to compose a text which would be useful as a reference work for the general practitioner and, at the same time, meet the needs of the undergraduate student of surgery. Anyone who peruses the text carefully will agree that the authors have given American surgery one of its best general texts in the field.

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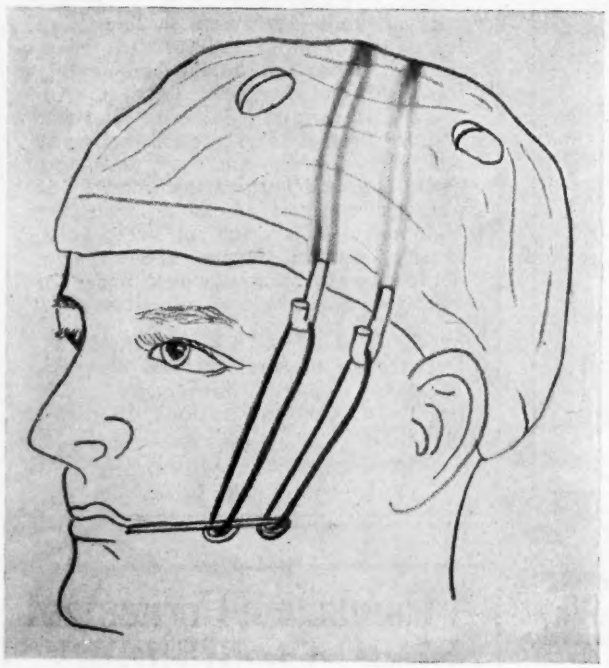

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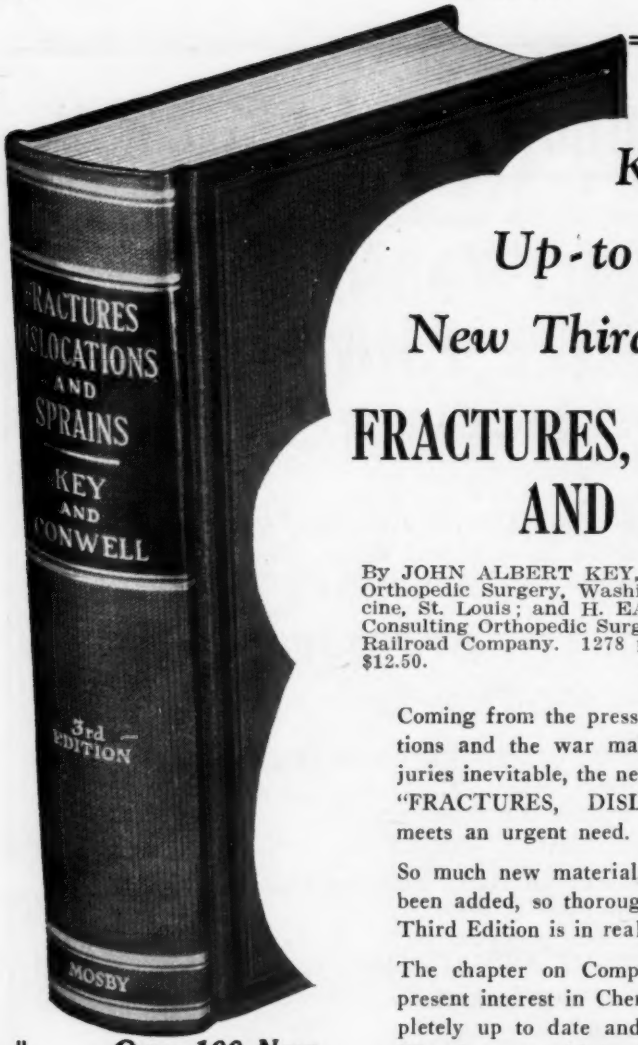

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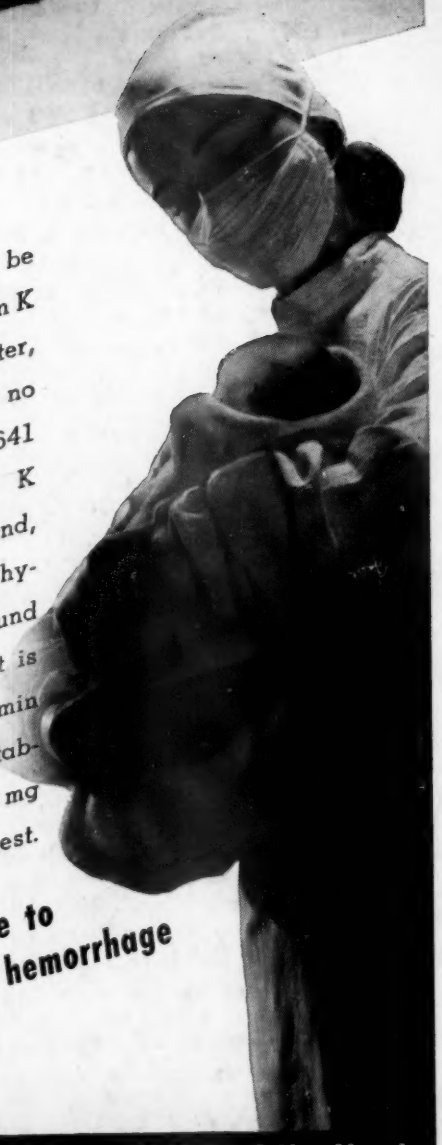

Hemorrhagic disorders in the newborn can be strikingly reduced by the administration of vitamin K to mothers during labor. Fitzgerald and Webster, J.A.M.A., 1942, 119:1082, report that there was no evidence of neonatal bleeding in a series of 641 babies whose mothers had received vitamin K therapy. Synkayvite, the Roche vitamin K-compound, is the choice of many physicians for routine prophylactic vitamin K therapy because of its all-round therapeutic efficiency. Molecule for molecule, it is one and one-half times as active as natural vitamin K, yet relatively nontoxic. Supplied in oral tablets, 5 mg each; and ampuls, 1 cc, 5 mg or 10 mg each. Literature will gladly be sent on request.

a routine measure to prevent neonatal hemorrhage

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